EXHIBIT A
FOLLOWS

CONTROLLED RELEASE ARGININE FORMULATIONS

RELATED APPLICATION DATA

This application is a continuation-in-part application of U.S. Serial No. 09/239,392 filed April 16, 1999 which is a continuation-in-part application of U.S. Serial No. 09/226,580 filed January 7, 1999, which is a continuation-in-part application of U.S. Serial No. 09/833,842 filed April 10, 1997, now U.S. Patent No. 5,968,983 dated October 19, 1999 which is a continuation-in-part application of U.S. Serial No. 08/693,882 filed August 5, 1996, now U.S. Patent No. 5,767,160 dated August 6, 1996, which is a continuation-in-part application of U.S. Serial No. 08/321,051 filed October 5, 1994, now U.S. Patent No. 5,543,430 dated June 16, 1998.

BACKGROUND OF THE INVENTION

A family of enzymes generically referred to as Nitric Oxide Synthase ("NOS") is responsible for forming to form nitric oxide from L-arginine. The nitric oxide produced is at least partially responsible for the endothelium dependent relaxation and activation of soluble guanylate cyclase, neurotransmission in the central and peripheral nervous systems, and activated macrophage cytotoxicity.

Nitric Oxide Synthase, occurs in many distinct isoforms which include a constitutive form (cNOS) and an inducible form (iNOS). The constitutive form is present in normal endothelial cells, neurons and some other tissues. Formation of nitric oxide by the constitutive form in endothelial cells is thought to play an important role in normal blood pressure regulation, prevention of endothelial dysfunction such as hyperlipodemia, arteriosclerosis, thrombosis, and restenosis. The inducible form of nitric oxide synthase has

EXHIBIT B
FOLLOWS

PTO-103X
(Rev. 6-99)

FILING RECEIPT

CORRECTED

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO.	DRWGS	TOT CL	IND CL
09/293,392	04/16/99	1614	$541.00	99-122-US	17	22	5

RAYMOND A MILLER
REED SMITH SHAW AND MCCLAY LLP
P O BOX 488
PITTSBURGH PA 15230-0488

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts of Application" ("Missing Parts Notice") in this application, please submit any corrections to this Filing Receipt with your reply to the "Missing Parts Notice." When the PTO processes the reply to the "Missing Parts Notice," the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s) WAYNE YH. KAESEMEYER, AUGUSTA, GA.

CONTINUING DATA AS CLAIMED BY APPLICANT-
THIS APPLN IS A CIP OF 09/226,580 01/07/99
WHICH IS A CIP OF 08/833,842 04/10/97
WHICH IS A CIP OF 08/693,882 08/05/96 PAT 5,767,160
WHICH IS A CIP OF 08/321,051 10/05/94 PAT 5,543,430

IF REQUIRED, FOREIGN FILING LICENSE GRANTED 05/12/99 ** SMALL ENTITY **
TITLE
THERAPEUTIC MIXTURE USEFUL IN INHIBITING LESION FORMATION AFTER VASCULAR INJURY

PRELIMINARY CLASS: 514

BJ 10-1-99

DATA ENTRY BY: GARNETT, SANDRA TEAM: 06 DATE: 09/23/99

(See reverse for new important information)

EXHIBIT C
FOLLOWS

Patent Application Information Retrieval

Order Certified Application As Filed Order Certified File Wrapper View Order List

09/239,392 VEHICLE INFLATOR WITH STORED GAS FOR SUPPLEMENTING INFLATION

Select New Case | Application Data | Transaction History | Continuity Data | Address & Attorney/Agent

Bibliographic Data

Application Number:	09/239,392	Customer Number:	-
Filing or 371 (c) Date:	01-28-1999	Status:	Expressly Abandoned -- During Examination
Application Type:	Utility	Status Date:	04-10-2000
Examiner Name:	BOTTORFF, CHRISTOPHER	Location:	FILE REPOSITORY (FRANCONIA)
Group Art Unit:	3611	Location Date:	04-15-2003
Confirmation Number:	6037	Earliest Publication No:	-
Attorney Docket Number:	2429-74	Earliest Publication Date:	-
Class / Subclass:	280/736	Patent Number:	-
First Named Inventor:	BRIAN K. HAMILTON , LITTLETON, CO (US)	Issue Date of Patent:	-

Title of Invention: VEHICLE INFLATOR WITH STORED GAS FOR SUPPLEMENTING INFLATION

If you need help:

- *Call the Patent Electronic Business Center at (866) 217-9197 (toll free) or e-mail EBC@uspto.gov for specific questions about Patent Application Information Retrieval (PAIR).*
- *Send general questions about USPTO programs to the USPTO Contact Center (UCC) .*
- *If you experience technical difficulties or problems with this application, please report them via e-mail to Electronic Business Support or call 1 800-786-9199.*

EXHIBIT D
FOLLOWS

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	Kaesemeyer, Wayne H.	Group Art Unit:(not yet assigned)
Serial No.:	05,599	Examiner Name: (not yet assigned)
Filing Date:	June 28, 2000	Docket No. 25795-2
Title:	CONTROLLED RELEASE ARGININE FORMULATIONS	

COMBINED DECLARATION AND POWER OF ATTORNEY

As the below named inventor, I hereby declare that:

This declaration is of the following type:

- x Original
- □ Design
- □ Supplemental
- □ National stage of PCT
- □ Divisional
- □ Continuation
- x Continuation-in-part

My residence, post office address, and citizenship are as stated below next to my name.

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

CONTROLLED RELEASE ARGININE FORMULATIONS

the specification of which is attached hereto, unless the following box is checked:

[x] was filed on June 28, 2000, as United States Application Number 09/605,599;
[] and was amended on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §§ 119(a) - (d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed:

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

Serial No. 09/293,392 filed April 16, 1999; Serial No. 09/226,580 filed January 7, 1999; Serial No. 09/833,842 filed April 10, 1997 (now U.S. Patent No. 5,968,983); Serial No. 08/693,882 filed August 5, 1996 (now U.S. Patent No. 5,767,160); and Serial No. 08/321,051 filed October 5, 1994 (now U.S. Patent No. 5,543,430).

As named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Raymond A. Miller, Reg. No. 42,891

Address all telephone calls to	:	Raymond A. Miller
at telephone number	:	(216) 363-4417
Address all correspondence to	:	Raymond A. Miller, Esq.

BENESCH, FRIEDLANDER, COPLAN & ARONOFF L.L.P.
2300 BP Tower
200 Public Square
Cleveland, Ohio 44114-2378

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor: Wayne H. KAESEMEYER

Inventor's signature: Wayne H. Kaesemeyer

Date: 10-13-00

Residence	:	Augusta, GA
Post Office Address	:	2433 McDowell Street Augusta, GA 30904
Citizenship	:	United States of America

EXHIBIT E
FOLLOWS

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/605,599	06/28/2000	1615	0	25795-2	8	20	3

FILING RECEIPT

Raymond A Miller Esq
Benesch Friedlander Coplan & Aronoff LLP
2300 BP Tower
200 Public Square
Cleveland, OH 44114-2378

OC000000005432990

Date Mailed: 09/27/2000

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the PTO processes the reply to the Notice, the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Wayne H. Kaesemeyer, Residence Not Provided;

Continuing Data as Claimed by Applicant

THIS APPLICATION IS A CIP OF 09/239,392 01/28/1999 ABN
WHICH IS A CIP OF 08/693,882 08/05/1996 PAT 5,767,160
WHICH IS A CIP OF 08/321,051 10/05/1994 PAT 5,543,430
AND SAID 09/239,392 01/28/1999
IS A CIP OF 09/226,580 01/07/1999
WHICH IS A CIP OF 08/833,842 04/10/1997 PAT 5,968,983

Foreign Applications

If Required, Foreign Filing License Granted 08/17/2000

Title

Controlled release arginine formulations

Preliminary Class

424

Data entry by : ABRANYOS, ASKALE Team : OIPE Date: 09/27/2000

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CRF 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 36 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Office of Export Administration, Department of Commerce (15 CFR 370.10 (j)); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15 (b).

PLEASE NOTE the following information about the Filing Receipt:

- The articles such as "**a**," "**an**" and "**the**" are not included as the first words in the title of an application. They are considered to be unnecessery to the understanding of the title.
- The words "**new**," "**Improved**," "**Improvements in**" or "**relating to**" are not included as first words in the title of an application because a patent application, by nature, is a new idea or improvement.
- The title may be truncated if it consists of more than 600 characters (letters and spaces combined).
- The docket number allows a maximum of 25 characters.
- If your application was submitted under 37 CFR 1.10, your filing date should be the "date in" found on the Express Mail label. If there is a discrepancy, you should submit a request for a corrected Filing Receipt along with a copy of the Express Mail label showing the "date in."
- The title is recorded in sentence case.

Any corrections that may need to be done to your Filing Receipt should be directed to:

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Office of Initial Patent Examination
Customer Service Center
Washington, DC 20231

EXHIBIT F
FOLLOWS

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Wayne H. Kaesemeyer	
Serial No.:	09/605,599	Art Unit: 1615
Filing Date:	June 28, 2000	
Title:	CONTROLLED RELEASE ARGININE FORMULATIONS	
Docket No.:	25795-2	

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to the examination of the above-identified application, it is requested that the following amendment be made.

IN THE SPECIFICATION:

Page 1, line 2, delete "09/239,392" and insert the following --09/293,392--.

REMARKS

The above amendment is a typographical error and correction is requested.

Also, please furnish the undersigned attorney of record with a corrected Official filing receipt evidencing this correction.

Respectfully submitted.

By: _____
Raymond A. Miller, Reg. No. 42891

Benesch, Friedlander,
Coplan & Aronoff LLP
200 Public Square
2300 BP Tower
Cleveland, Ohio 44114
(216) 363-4417

November 7, 2000

EXHIBIT G
FOLLOWS

NO.

Pat. No. ______
Inventor/Applicant: Wayne H. Kaesemeyer Ser. No. 09/605,599
Title Controlled Release Arginine Form Filed 6-28-2000
Attorney Docket No. 25795-2 Initials RMM/dp Date 11-7-00

☐ PATENT/DESIGN APPLICATION
___ New Application Transmittal
___ Cont. ___ Div. ___ C-I-P ___ Provisional
✓ Declaration/Power of Atty.
___ pgs. Specification
___ pgs. Claims
___ total ___ independent
___ pgs. Abstract
___ Sheet(s) of drawing(s)
___ formal ___ informal
✓ Preliminary Amendment
___ Claim for Right of Priority
___ Priority document(s)
2 Small Entity Statement
___ Final Fee
✓ Response to missing parts

☑ ASSIGNMENT
✓ Transmittal ___ Confirmatory

☐ INFORMATION DISCLOSURE STATEMENT
___ PTO Form 1449 ___ Refs.

☐ CHECK(S) in Amount $ ______

☐ AMENDMENT (Due ______)
___ Transmittal(s)
___ Extension of Time (For ___ month(s))

☑ OTHER Request for Corrected Filing Receipt

RECEIPT IS HEREBY ACKNOWLEDGED

OIPE
NOV 0 9 2000
PATENT & TRADEMARK OFFICE

EXHIBIT H
FOLLOWS

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/605,599	06/28/2000	1615	420	25795-2	8	20	3

Raymond A Miller Esq
Benesch Friedlander Coplan & Aronoff LLP
2300 BP Tower
200 Public Square
Cleveland, OH 44114-2378

FILING RECEIPT

'OC000000005822073'

Date Mailed: 03/02/2001

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the PTO processes the reply to the Notice, the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Wayne H. Kaesemeyer, Augusta, GA ;

Continuing Data as Claimed by Applicant

THIS APPLICATION IS A CIP OF 09/239,392 01/28/1999 ABN
WHICH IS A CIP OF 08/693,882 08/05/1996 PAT 5,767,160
WHICH IS A CIP OF 08/321,051 10/05/1994 PAT 5,543,430
AND SAID 09/239,392 01/28/1999
IS A CIP OF 09/226,580 01/07/1999
WHICH IS A CIP OF 08/833,842 04/10/1997 PAT 5,968,983

Foreign Applications

If Required, **Foreign Filing License Granted** 08/17/2000

**** SMALL ENTITY ****

Title

Controlled release arginine formulations

Preliminary Class

424

Data entry by : HALLMAN, LINDA Team : 2800 Date: 03/02/2001

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CRF 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 36 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Office of Export Administration, Department of Commerce (15 CFR 370.10 (j)); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15 (b).

PLEASE NOTE the following information about the Filing Receipt:

- The articles such as "**a**," "**an**" and "**the**" are not included as the first words in the title of an application. They are considered to be unnecessary to the understanding of the title.
- The words "**new**," "**improved**," "**improvements in**" or "**relating to**" are not included as first words in the title of an application because a patent application, by nature, is a new idea or improvement.
- The title may be truncated if it consists of more than 600 characters (letters and spaces combined).
- The docket number allows a maximum of 25 characters.
- If your application was submitted under 37 CFR 1.10, your filing date should be the "date in" found on the Express Mail label. If there is a discrepancy, you should submit a request for a corrected Filing Receipt along with a copy of the Express Mail label showing the "date in."
- The title is recorded in sentence case.

Any corrections that may need to be done to your Filing Receipt should be directed to:

Assistant Commissioner for Patents
Office of Initial Patent Examination
Customer Service Center
Washington, DC 20231

EXHIBIT I
FOLLOWS

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

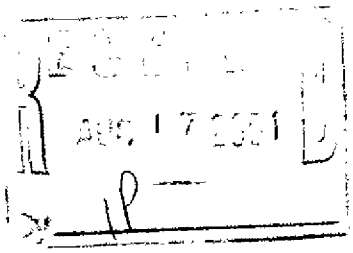
APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

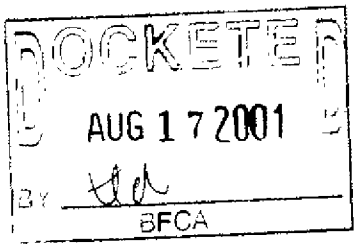
EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks





Office Action Summary	Application No.	Applicant(s)	
	09/605,599	KAESEMEYER, WAYNE H.	
	Examiner	Art Unit	
	Dwayne C Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Claims

1. Claims 1-20 are pending.

2. Claims 1-20 are rejected.

Specification

3. The disclosure is objected to because of the following informalities: the top of each page is of the specification and claims are missing sections due to a two-hole punch.

Appropriate correction is required.

1. A substitute specification along with the claims is required pursuant to 37 CFR 1.125(a) because the top of each page is of the specification and claims is missing sections due to a two-hole punch.

A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

3. Claims 1-20 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Usala of U.S. Patent No. 5,824,331. Usala teaches of a composition containing L-arginine in a sustained-polymeric release matrix., (see abstract, columns 2-4, and claims 1-51).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (703) 308-4634. The examiner can normally be reached on Mondays through Fridays from 8:30 am to 6:00 pm. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

DWAYNE C. JONES
PRIMARY EXAMINER
Tech. Ctr. 1614
August 10, 2001

EXHIBIT J
FOLLOWS

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application:	Kaesemeyer, Wayne H.	Group Art Unit:	1614
Serial No.:	09/605,599	Examiner:	Jones, Dwayne
Filing Date:	June 28, 2000	Docket No.:	25795-2
Title:	CONTROLLED RELEASE ARGININE FORMULATIONS		

Box NON FEE Amendment
Commissioner for Patents
Washington, D.C. 20231

AMENDMENT AND RESPONSE TO FIRST OFFICE ACTION

Dear Sir:

This response addresses the issues raised in the August 15, 2001 Office Action in the above-identified application. The three-month period for replying to this Office Action expires on November 15, 2001. Accordingly, this Amendment and Response is timely filed. Please review the above-identified applications in view of the following amendments and remarks.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commissioner of Patents
Washington, D.C. 20231, on _____

_____
Signature

AMENDMENTS

IN THE SPECIFICATION:

A substitute specification along with the claims is submitted under 37 C.F.R. §1.125(a) since the top of each page of the original specification and claims was missing sections due to a two-hole punch. No new matter was added to the specification.

IN THE CLAIMS:

Please substitute claim 1 for the pending claim having the same claim number.

1. (Amended) A method for producing extended-release tablets comprising the steps of: mixing a therapeutically effective amount of L-arginine with a sustained release matrix; and compressing said mixture to form tablets.

Please substitute claim 2 for the pending claim having the same claim number.

2. (Amended) The method of claim 1, wherein said L-arginine is selected from the group consisting of L-arginine hydrochloride, pharmacologically acceptable L-arginine salts, and mixtures thereof.

Please substitute claim 13 for the pending claim having the same claim number.

13. (Amended) A composition comprised of a therapeutically effective amount of L-arginine; and a sustained release polymeric matrix.

Please substitute claim 14 for the pending claim having the same claim number.

14. (Amended) The composition of claim 13, further including a nitrate.

Please substitute claim 16 for the pending claim having the same claim number.

16. (Amended) An extended-release pharmaceutical tablet comprised of a sustained release matrix and a therapeutically effective amount of L-arginine.

REMARKS

Applicant appreciates the careful consideration given to this case by the Examiner. For the Examiner's convenience, Applicant will address the issues raised in the Office Action in the order that they appear.

The Examiner has requested a substitute specification due to the presence of hole punches in the original specification. Applicant submits herewith a substitute specification pursuant to 37 C.F.R. §1.125. No new matter is contained in the substitute specification. A marked-up version showing the changes to the specification is attached hereto. The marked up version of the claims is provided separately.

Claims 1-20 stand rejected under 35 U.S.C. §102(e) as being clearly anticipated U.S. Patent No. 5,824,331 to Usala ("Usala"). The claims of the present application have been amended to reflect this difference. All of the claims have been amended to specifically recite "therapeutically effective amounts of L-arginine". It is respectfully pointed out that the "arginine analogs" of Usala are the exact opposite of what is being claimed by the applicant. The arginine analogs of Usala are nitric oxide *inhibitors* and scavengers (e.g. D-arginine) (see portion of Usala bridging columns 22-23). L-arginine acts as a *substrate* of NOS with resulting increase in production of nitric oxide (see page 4, lines 13-19 of the present application). Although Usala does teach of a composition of a matrix containing an arginine analog, the arginine analog as defined by Usala is not an equivalent and does not anticipate the claims, particularly as amended. Accordingly, it is respectfully submitted that rejection of claims 1-20 under 35 U.S.C. §102(e) on the basis as being clearly anticipated by Usala should be withdrawn.

In view of the remarks presented above, it is believed that claims 1-20 are in condition for final allowance and notice to such effect is courteously requested. Should the examiner have any additional comments or concerns regarding this case, he is invited to contact the undersigned at his convenience to address those issues.

Respectfully submitted,

Dated: November 15, 2001

By: _____

Raymond A. Miller
Reg. No. 42,891

BENESCH, FRIEDLANDER,
COPLAN & ARONOFF LLP
2300 BP Tower
200 Public Square
Cleveland, OH 44114-2378
(216) 363-4417

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

A substitute specification along with the claims is submitted under 37 C.F.R. §1.125(a) since the top of each page of the original specification and claims was missing sections due to a two-hole punch. No new matter was added to the specification.

IN THE CLAIMS:

Please substitute claim 1 for the pending claim having the same claim number.

1. (Amended) A method for producing extended-release tablets comprising the steps of: mixing **a therapeutically effective amount of L-arginine [arginine]** with a sustained release matrix; and compressing said mixture to form tablets.

Please substitute claim 2 for the pending claim having the same claim number.

2. (Amended) The method of claim 1, wherein said L-arginine is selected from the group consisting of L-arginine **hydrochloride [hydrochlorie]**, pharmacologically acceptable L-arginine salts, and mixtures thereof.

Please substitute claim 13 for the pending claim having the same claim number.

13. (Amended) A composition comprised of **a therapeutically effective amount of L-arginine [arginine]**; and a sustained release polymeric matrix.

Please substitute claim 14 for the pending claim having the same claim number.

14. (Amended) The composition of claim 13, further including a nitrate**.[,]**

Please substitute claim 16 for the pending claim having the same claim number.

16. (Amended) An extended-release pharmaceutical tablet comprised of a sustained release matrix and **a therapeutically effective amount of L-arginine [arginine]**.

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application:	Kaesemeyer, Wayne H.	Group Art Unit:	1614
Serial No.:	09/605,599	Examiner:	Jones, Dwayne
Filing Date:	June 28, 2000	Docket No.:	25795-2
Title:	CONTROLLED RELEASE ARGININE FORMULATIONS		

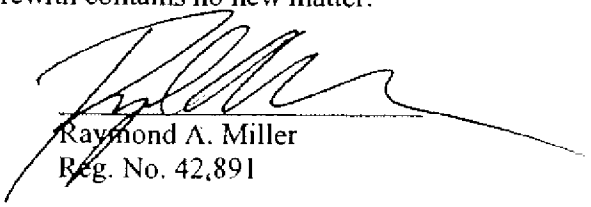
Box NON FEE Amendment
Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF SUBSTITUTE SPECIFICATION (37 C.F.R. §1.125)

Dear Sir:

Enclosed is a substitute specification for the originally filed specification in this application. This substitute specification is being voluntarily submitted, in order to facilitate the processing of the above-identified application. Also enclosed is a marked-up version of the originally filed specification showing the matter being added to and the matter being deleted from the specification. Accompanying this transmittal is a statement, as required by 37 C.F.R. §1.125, that the substitute specification transmitted herewith contains no new matter.

Dated: November 15, 2001



Raymond A. Miller
Reg. No. 42,891

BENESCH, FRIEDLANDER,
COPLAN & ARONOFF LLP
2300 BP Tower
200 Public Square
Cleveland, OH 44114-2378
(216) 363-4417

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application:	Kaesemeyer, Wayne H.	Group Art Unit:	1614
Serial No.:	09/605,599	Examiner:	Jones, Dwayne
Filing Date:	June 28, 2000	Docket No.:	25795-2
Title:	CONTROLLED RELEASE ARGININE FORMULATIONS		

Box NON FEE Amendment
Commissioner for Patents
Washington, D.C. 20231

STATEMENT THAT SUBSTITUTE SPECIFICATION

CONTAINS NO NEW MATTER

Dear Sir:

I hereby state that the accompanying substitute specification contains no new matter over that contained in the above-identified application originally filed. I further state that the changes made are the same as indicated in the accompanying marked-up version showing the changes made to the originally filed specification.

I am an agent under 37 C.F.R. §1.34(a).

Dated: November 15, 2001

Raymond A. Miller
Reg. No. 42,891

BENESCH, FRIEDLANDER,
COPLAN & ARONOFF LLP
2300 BP Tower
200 Public Square
Cleveland, OH 44114-2378
(216) 363-4417

EXHIBIT K
FOLLOWS

SUBSTITUTE SPECIFICATION

CONTROLLED RELEASE ARGININE FORMULATIONS

RELATED APPLICATION DATA

This application is a continuation-in-part application of U.S. Serial No. 09/239,392 filed April 16, 1999 which is a continuation-in-part application of U.S. Serial No. 09/226,580 filed January 7, 1999, which is a continuation-in-part application of U.S. Serial No. 09/833,842 filed April 10, 1997, now U.S. Patent No. 5,968,983 dated October 19, 1999 which is a continuation-in-part application of U.S. Serial No. 08/693,882 filed August 5, 1996, now U.S. Patent No. 5,767,160 dated August 6, 1996, which is a continuation-in-part application of U.S. Serial No. 08/321,051 filed October 5, 1994, now U.S. Patent No. 5,543,430 dated June 16, 1998.

BACKGROUND OF THE INVENTION

A family of enzymes generically referred to as Nitric Oxide Synthase ("NOS") is responsible for forming nitric oxide from L-arginine. The nitric oxide produced is at least partially responsible for the endothelium dependent relaxation and activation of soluble guanylate cyclase, neurotransmission in the central and peripheral nervous systems, and activated macrophage cytotoxicity.

Nitric Oxide Synthase, occurs in many distinct isoforms which include a constitutive form (cNOS) and an inducible form (iNOS). The constitutive form is present in normal endothelial cells, neurons and some other tissues. Formation of nitric oxide by the constitutive form in endothelial cells is thought to play an important role in normal blood pressure regulation, prevention of endothelial dysfunction such as hyperlipodemia, arteriosclerosis, thrombosis, and restenosis. The inducible form of nitric oxide synthase has

EXHIBIT L
FOLLOWS

DETAILED ACTION

Status of Claims

1. Claims 1-20 are pending.

2. Claims 1-20 are rejected.

Response to Arguments

3. Applicant's arguments filed January 3, 2002 have been fully considered but they are not persuasive with respect to composition claims 13-20. Applicants argue that Usala analogs are inhibitors of scavengers and also that the instant claims have been amended to recite "therapeutically effective amounts of L-arginine".

4. In response to applicant's first argument that Usala analogs are inhibitors of scavengers, it is noted that claims 13-20 are composition claims and accordingly an intended use of composition claims does not provide patentable distinction over the prior art. Applicant attempted to limit the composition claims with the incorporation of the phrase "therapeutically effective amounts of L-arginine". However, it is noted that Usala also teaches of a therapeutic composition, which contains the amino acid of L-arginine, and that it contains an effective amount of the L-arginine, (see column 16, 12-13).

Specification

5. The substitute specification of January 3, 2002 has been received and entered.

Sub Spec ent

EXHIBIT M
FOLLOWS

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 25795-2

Box No. I TITLE OF INVENTION

Controlled Release Arginine Formulations

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

NITROSYSTEMS, Inc.
Trowbridge House
512 Telfair Street
Augusta, GA 30901
US

Telephone No. (706) 724-4565

Facsimile No. (706) 724-1132

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KAESEMEYER, Wayne H.
2433 McDowell Street
Augusta, GA 30901
US

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MILLER, Raymond A.
BENESCH, FRIEDLANDER, COPLAN & ARONOFF LLP
2300 BP Tower
200 Public Square
Cleveland, Ohio 44114-2378
US

Telephone No. 216-363-4417

Facsimile No. 216-363-4588

Teleprinter No.

Agent's registration No. with the Office 42,891

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☒ AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ EP **European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ AE United Arab Emirates
☒ AG Antigua and Barbuda
☒ AL Albania
☒ AM Armenia
☒ AT Austria
☒ AU Australia
☒ AZ Azerbaijan
☒ BA Bosnia and Herzegovina
☒ BB Barbados
☒ BG Bulgaria
☒ BR Brazil
☒ BY Belarus
☒ BZ Belize
☒ CA Canada
☒ CH & LI Switzerland and Liechtenstein
☒ CN China
☒ CO Colombia
☒ CR Costa Rica
☒ CU Cuba
☒ CZ Czech Republic
☒ DE Germany
☒ DK Denmark
☒ DM Dominica
☒ DZ Algeria
☒ EE Estonia
☒ ES Spain
☒ FI Finland
☒ GB United Kingdom
☒ GD Grenada
☒ GE Georgia
☒ GH Ghana
☒ GM Gambia
☒ HR Croatia
☒ HU Hungary
☒ ID Indonesia
☒ IL Israel
☒ IN India
☒ IS Iceland
☒ JP Japan
☒ KE Kenya
☒ KG Kyrgyzstan
☒ KP Democratic People's Republic of Korea
☒ KR Republic of Korea
☒ KZ Kazakhstan
☒ LC Saint Lucia
☒ LK Sri Lanka
☒ LR Liberia
☒ LS Lesotho
☒ LT Lithuania
☒ LU Luxembourg
☒ LV Latvia
☒ MA Morocco
☒ MD Republic of Moldova
☒ MG Madagascar
☒ MK The former Yugoslav Republic of Macedonia
☒ MN Mongolia
☒ MW Malawi
☒ MX Mexico
☒ MZ Mozambique
☒ NO Norway
☒ NZ New Zealand
☒ PL Poland
☒ PT Portugal
☒ RO Romania
☒ RU Russian Federation
☒ SD Sudan
☒ SE Sweden
☒ SG Singapore
☒ SI Slovenia
☒ SK Slovakia
☒ SL Sierra Leone
☒ TJ Tajikistan
☒ TM Turkmenistan
☒ TR Turkey
☒ TT Trinidad and Tobago
☒ TZ United Republic of Tanzania
☒ UA Ukraine
☒ UG Uganda
☒ US United States of America
☒ UZ Uzbekistan
☒ VN Viet Nam
☒ YU Yugoslavia
☒ ZA South Africa
☒ ZW Zimbabwe

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ ..... ☐ ..... ☐ .....
☐ ..... ☐ ..... ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 28 June 2000	09/605,599	US	USPTO	
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* *Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* .....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA / USPTO .....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):*

Number of declarations

☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of **sheets** in **paper** form:

request (including declaration sheets)	:	4
description (excluding sequence listing part)	:	25
claims	:	2
abstract	:	1
drawings	:	8
Sub-total number of sheets	:	40
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:	0
Total number of sheets	:	40

(b) sequence listing part of description filed in **computer readable form**

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*: .....

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:	Number of items
1. ☒ fee calculation sheet	1
2. ☐ original separate power of attorney	
3. ☐ original general power of attorney	
4. ☐ copy of general power of attorney; reference number, if any:	
5. ☐ statement explaining lack of signature	
6. ☐ priority document(s) identified in Box No. VI as item(s):	
7. ☐ translation of international application into *(language)*:	
8. ☐ **separate** indications concerning deposited microorganism or other biological material	
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))	
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	
(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	
10. ☒ other *(specify)*: postcard,cert. of express mail,check	

Figure of the **drawings** which should accompany the abstract: Fig. 1A

Language of **filing** of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Raymond A. Miller, Agent

28 June 2001

For receiving Office use only

1. Date of actual receipt of the purported international application:

2. Drawings:
   ☐ received:
   ☐ not received:

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority (if two or more are competent): ISA /

6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

EXHIBIT N
FOLLOWS

To: Commissioner for Patents
BOX PCT
Washington, DC 20231

Atty: Raymond A. Miller
U.S. Express Mail No. EU200162468 US
Deposited: October 24, 2002

In re Application of NitrOSystems, Inc., et al.
Serial No. Not Yet Assigned

Atty. Docket No.126245.202

Kindly affix hereon the official stamp of the U.S. Patent and Trademark Office acknowledging receipt of the following:

[X] Transmittal Letter to the U.S. Designated/Elected Office concerning a filing under 35 U.S.C. 371
[X] Check in the Amount of $355.00
[X] Authorization to Charge Deposit Account for Additional Fees

10/258633
DT05 Rec'd PCT/PTO 24 OCT 2002

Date Received:_____

EXHIBIT O
FOLLOWS

CONTROLLED RELEASE ARGININE FORMULATIONS

RELATED APPLICATION DATA

This application is a continuation-in-part application of U.S. Serial No. 09/239,392 filed April 16, 1999 which is a continuation-in-part application of U.S. Serial No. 09/226,580 filed January 7, 1999, which is a continuation-in-part application of U.S. Serial No. 09/833,842 filed April 10, 1997, now U.S. Patent No. 5,968,983 dated October 19, 1999 which is a continuation-in-part application of U.S. Serial No. 08/693,882 filed August 5, 1996, now U.S. Patent No. 5,767,160 dated August 6, 1996, which is a continuation-in-part application of U.S. Serial No. 08/321,051 filed October 5, 1994, now U.S. Patent No. 5,543,430 dated June 16, 1998.

BACKGROUND OF THE INVENTION

A family of enzymes generically referred to as Nitric Oxide Synthase ("NOS") is responsible for forming to form nitric oxide from L-arginine. The nitric oxide produced is at least partially responsible for the endothelium dependent relaxation and activation of soluble guanylate cyclase, neurotransmission in the central and peripheral nervous systems, and activated macrophage cytotoxicity.

Nitric Oxide Synthase, occurs in many distinct isoforms which include a constitutive form (cNOS) and an inducible form (iNOS). The constitutive form is present in normal endothelial cells, neurons and some other tissues. Formation of nitric oxide by the constitutive form in endothelial cells is thought to play an important role in normal blood pressure regulation, prevention of endothelial dysfunction such as hyperlipodemia, arteriosclerosis, thrombosis, and restenosis. The inducible form of nitric oxide synthase has

EXHIBIT P
FOLLOWS

PATENT APPLICATION
Application No. 10/258,633
Attorney Docket No. 126625.00710

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/258,633
Applicant	:	Wayne H. Kaesemeyer
Filed	:	May 6, 2003
Group Art Unit	:	1618
Examiner	:	James William Rogers
Docket No.	:	126625.00710
Confirmation No.	:	3645

Title: CONTROLLED RELEASE ARGININE FORMULATIONS

PETITION TO ACCEPT AN UNINTENTIONALLY DELAYED CLAIM OF PRIORITY UNDER 37 C.F.R. §1.78(a)(3)

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA. 22313-1450

Examiner:

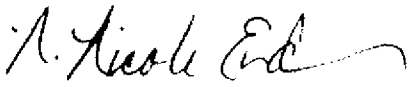
Applicant respectfully requests that the claim of priority recited in the first paragraph of the specification of the above-referenced application be amended pursuant to 37 C.F.R. §1.78(a)(2)(i) and (ii) to include the claim of priority to U.S. Non-Provisional Application No. 09/605,599, filed June 28, 2000. Applicants submit concurrently herewith the priority document for U.S. Non-Provisional Application No. 09/605,599. The amended claim of priority is presented on page 3 of this Petition. An Application Data Sheet stating the relationship of the prior-filed applications to the instant application in compliance with 37 C.F.R. §1.78(a)(2)(i) is also filed concurrently herewith.

Pursuant to 37 C.F.R. §1.78(a)(2)(i) and (ii), a reference to be included in the specification claiming benefit of prior applications must be submitted during the pendency of the application, which requirement is met in the present circumstances. However, the present benefit

claim is being presented after the time period provided by 37 C.F.R. §1.78(a)(2)(ii). Accordingly, Applicants hereby petition the Commissioner under 37 C.F.R. §1.78(a)(3) to accept the present unintentionally delayed benefit claim.

The entire delay in filing this benefit claim under 37 C.F.R. §1.78(a)(2)(ii) was unintentional. Payment of the fee of $1,410.00 set forth in 37 C.F.R. §1.17(t) is being submitted herewith. In addition, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment or refund to Deposit Account No. 50-0436.

Respectfully Submitted,



By:_____
N. Nicole Endejann
Reg. No. 50,229

Pepper Hamilton LLP
One Mellon Center, 50th Floor
500 Grant Street
Pittsburgh, PA 15219
Telephone No.: (412) 454-5869
Facsimile No.: (412) 281-0717
Date: May 6, 2009

AMENDMENT TO SPECIFICATION - PRIORITY CLAIM

Please amend the first paragraph after the title "RELATED APPLICATION DATA" on page 1 of the specification as follows:

This application is a U.S. national stage of international application PCT/US2001/20887 (WO 02/00212) filed June 28, 2001, which claims the benefit of priority to U.S. Application No. 09/605,599 filed June 28, 2000, now abandoned. This application is a continuation-in-part application of U. S. Serial No. 09/239,392 filed April 16,1999 which is a continuation-in-part application of U. S. Serial No. 09/226,580 filed January 7,1999, which is a continuation-in-part application of U. S. Serial No. 09/833,842 filed April 10,1997, now U. S. Patent No. 5,968,983 dated October 19,1999 which is a continuation-in-part application of U. S. Serial No. 08/693,882 filed August 5, 1996, now U.S. Patent No. 5,767,160 dated August 6,1996, which is a continuation-in-part application of U. S. Serial No. 08/321,051 filed October 5,1994, now U. S. Patent No. 5,543,430 dated June 16,1998, the contents of which are incorporated herein by reference in its entirety.

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	126625.00710
	Application Number	
Title of Invention	CONTROLLED RELEASE ARGININE FORMULATIONS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Wayne	H.	Kaesemeyer	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Augusta	State/Province	GA	Country of Residence	US

Citizenship under 37 CFR 1.41(b) US

Mailing Address of Applicant:

Address 1	1021 15th Street
Address 2	

City	Augusta	State/Province	GA
Postal Code	30901	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence information of this application.**

Customer Number	21269		
Email Address	docketingpgh@pepperlaw.com	Add Email	Remove Email

Application Information:

Title of the Invention	CONTROLLED RELEASE ARGININE FORMULATIONS		
Attorney Docket Number	126625.00710	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	8	Suggested Figure for Publication (if any)	

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	126625.00710
	Application Number	
Title of Invention	CONTROLLED RELEASE ARGININE FORMULATIONS	

Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	**Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	21269		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	a 371 of international	PCT/US2001/20887	2001-06-28
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US2001/20887	Continuation in part of	09605599	2000-06-28

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			◉ Yes ○ No

Additional Foreign Priority Data may be generated within this form by selecting the Add button.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	126625.00710
	Application Number	
Title of Invention	CONTROLLED RELEASE ARGININE FORMULATIONS	

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1

If the Assignee is an Organization check here. ☒

Organization Name	PALMETTO PHARMACEUTICALS, LLC		
Mailing Address Information:			
Address 1	217 MEDINAH		
Address 2			
City	SAINT SIMONS ISLAND	**State/Province**	GA
Country	US	Postal Code	31522
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the Add button.

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/N. Nicole Endejann/			Date (YYYY-MM-DD)	2009-05-06
First Name	N. Nicole	Last Name	Endejann	Registration Number	50229

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent applicabon or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of racords may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

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3. A record in this system of records may be disclosed, as a routine usa, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may ba disclosed, as a roubne use, to the Intemational Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosad, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of racords may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PI 446911

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

August 11, 2001

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: *09/603,399*
FILING DATE: *June 28, 2000*
PCT APPLICATION NUMBER: *PCT/US01/20887*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

Andrea T Jones
ANDREA T JONES
Certifying Officer

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06-29-00

A

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June 28, 2000

VIA EXPRESS MAIL LABEL NO. EM016593006US

Assistant Commissioner of Patents
Box Patent Application
Washington, DC 20231

Re: New U.S. Patent Application
Inventor: Wayne H. Kaesemeyer
For "CONTROLLED RELEASE ARGININE FORMULATIONS"
Our Docket No.: 25795-2

Dear Sir:

Enclosed are the following for filing in connection with the above-referenced new patent application:

1. A new patent application having 25 pages, including 21 pages of specification, 3 pages of claims, 1 page of abstract and 8 sheets of informal drawings;

2. An Express Mail Certificate; and

3. A self-addressed, stamped postcard, return of which is requested to acknowledge receipt of the enclosed documents.

No fees are being paid at this time, pending receipt of a Notice to File Missing Parts.

Please send all correspondence to:

RAYMOND A. MILLER, ESQ.
Reg. No. 42,891
Benesch, Friedlander, Coplan & Aronoff LLP
2300 BP Tower
200 Public Square
Cleveland, Ohio 44114-2378

Phone No.: 216-363-4417

Very truly yours,

BENESCH, FRIEDLANDER,
COPLAN & ARONOFF LLP

Raymond A. Miller
Reg. No. 42,891

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Wayne H. Kaesemeyer

Serial No.: New Patent Application

Filing Date: June 28, 2000 Docket No.: 25795-2

Title: CONTROLLED RELEASE ARGININE FORMULATIONS

CERTIFICATE OF EXPRESS MAIL UNDER 37 C.F.R. 1.10*

I hereby certify that this correspondence is being deposited with the United States Postal Service oo June 28, 2000, in an envelope as "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 C.F.R. 1.10, and addressed to Box PATENT APPLICATION, The Assistant Commissioner for Patents, Washington, D.C. 20231.

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CONTROLLED RELEASE ARGININE FORMULATIONS

RELATED APPLICATION DATA

This application is a continuation-in-part application of U.S. Serial No. 09/239,392 filed April 16, 1999 which is a continuation-in-part application of U.S. Serial No. 09/226,580 filed January 7, 1999, which is a continuation-in-part application of U.S. Serial No. 09/833,842 filed April 10, 1997, now U.S. Patent No. 5,968,983 dated October 19, 1999 which is a continuation-in-part application of U.S. Serial No. 08/693,882 filed August 5, 1996, now U.S. Patent No. 5,767,160 dated August 6, 1996, which is a continuation-in-part application of U.S. Serial No. 08/321,051 filed October 5, 1994, now U.S. Patent No. 5,543,430 dated June 16, 1998.

BACKGROUND OF THE INVENTION

A family of enzymes generically referred to as Nitric Oxide Synthase ("NOS") is responsible for forming to form nitric oxide from L-arginine. The nitric oxide produced is at least partially responsible for the endothelium dependent relaxation and activation of soluble guanylate cyclase, neurotransmission in the central and peripheral nervous systems, and activated macrophage cytotoxicity.

Nitric Oxide Synthase, occurs in many distinct isoforms which include a constitutive form (cNOS) and an inducible form (iNOS). The constitutive form is present in normal endothelial cells, neurons and some other tissues. Formation of nitric oxide by the constitutive form in endothelial cells is thought to play an important role in normal blood pressure regulation, prevention of endothelial dysfunction such as hyperlipodemia, arteriosclerosis, thrombosis, and restenosis. The inducible form of nitric oxide synthase has

been found to be present in activated macrophages and is induced in vascular smooth muscle cells, for example, by various cytokines and/or microbial products.

Although it was initially described in endothelium, NOS activity has now been described in many cell types. Brain, endothelium, and macrophage isoforms appear to be products of a variety of genes that have approximately 50% amino acid identity. NOS in brain and in endothelium have very similar properties, the major differences being that brain NOS is cytosolic and the endothelial enzyme is mainly a membrane-associated protein.

Sustained release products are widely recognized in the art and are of extreme importance in the pharmaceutical field. Through the use of such products, orally and rectally administered medications can be delivered continuously at a substantially uniform rate over a prolonged period of time so as to provide a stable, predetermined concentration of a drug in the bloodstream, without requiring close monitoring and frequent re-administration.

Sustained release is achieved by a variety of methods. Two common methods are: 1) providing a sustained release coating upon tablets or microspheres wherein slow release of the active occurs via either gradual permeation through or gradual breakdown of this coating; or 2) providing a sustained release matrix, such as a fat, a wax, or a polymeric material intermixed with the active ingredient in the tablet itself. These are described for example in "Sustained Action Dosage Forms" *The Theory and Practice of Industrial Pharmacy*, Manford Robinson ch. 14 (L. Lachman et al., eds., 2d ed., 1976) which is incorporated herein by reference thereto.

Sustained release matrix formulations are typically prepared by methods involving pre-granulating the active ingredient together with the matrix material via a wet granulation, solvent granulation, shear-melt or roto-melt granulation, or a wet pre-adsorption technique. In these techniques, a liquid phase is used in order to uniformly mix and/or closely contact the ingredients together so as to provide an evenly distributed matrix in intimate association with the active ingredient. These formation processes help prevent creation of interspersed quick-release zones which would result in discontinuous dissolution of the tablet and thus cause bioconcentration spikes of active ingredient in the patient. They frequently also

result in tablets of a relatively higher density than the dry mixed ones, thus allowing the use of tablets, for a given dose, that are smaller than those made by dry mixing for the same intended release rate.

U.S. Pat. No. 4,259,314 to Lowey employs a mixture of cellulose ethers--hydroxypropylmethylcellulose ("HPMC") and hydroxypropyl cellulose--to form a sustained release matrix in which the cellulose ether mixture has a weighted average viscosity rating of 250-4500

U.S. Pat. No. 5,451,409 to Rencher et al. discloses a dry mixed tablet in which a mixture of hydroxypropyl cellulose and hydroxyethyl cellulose forms the sustained release matrix; 0.5-10% HPMC is also added as a binder.

U.S. Pat. No. 4,369,172; U.S. Pat. No. 4,389,393, & U.S. Pat. No. 4,983,396 to Forest discuss the use of HPMC in a variety of formulations.

SUMMARY OF THE INVENTION

The administration of L-arginine alone has been shown to restore vascular NO activity in aminals and in humans with vasodilator dysfunction. The use of L-arginine or its biological equivalents alone and in combination with a variety of NOS agonist have been shown to have an unexpected beneficial effect. U.S. Patent No. 5,543,430; U.S. Patent No. 5,767,160; & U.S. Patent No. 5,968,983 all of which are specifically incorporated herein in their entirety by reference thereto discuss some of these formulations; their applications; and the benefits seen with the administration of these active ingredients. The therapeutic value of L-arginine when mixed with certian other agents is clear.

The present invention relates to L-arginine (for example and preferably L-arginine hydrochloride) formulated in a controlled release or sustained release formulation. Generally a carrier base material is combined with L-arginine, alone or in combination with another agent (e.g. nitrates, statins, etc.) which stimulates the production of Nitric Oxide. The ingredient(s) are manipulated into a solid, shaped dosage unit having a long-lasting and regular incremental

release of the L-arginine or other medicant. The preferred embodiment of the present invention uses HPMC as carrier base material. It would appear that a sustained released formulation of L-arginine either alone or in combination with other an agent which enhances the biotransformation of L-arginine or a NOS agonist (e.g. nitrates or Hmg-CoA reductase inhibitors such as pravastatin) would have a heretofore unexpected benefit.

The term "subject" as used herein means any mammal, including humans, where nitric oxide ("NO") formation from arginine occurs. The methods described herein contemplate prophylactic use as well as curative use in therapy of an existing condition. The term "native NO" as used herein refers to nitric oxide that is produced through the bio-transformation of L-arginine or in the L-arginine dependent pathway. The term "endpoints" as used herein refers to clinical events encountered in the course of treating cardiovascular disease, up to and including death (mortality).

"L-arginine" as used herein is intended to includes all biochemical equivalents (*i.e.*, salts, precursors, and its basic form) of L-arginine, preferably those that act as substrates of NOS with resulting increase in production of NO. For example, L-lysine may be a biological equivalent of L-arginine. Other bio-equivalents of L-arginine may include arginase inhibitors, citrulline, ornithine, and hydralazine. As used herein a "biological equivalent" is an agent or composition, or combination thereof, which has a similar biological function or effect as the agent or composition to which it is being deemed equivalent.

"Agonist" refers to an agent which stimulates or enhances the bio-transformation of a NO precursor, such as L-arginine or L-lysine to NO either through enzymatic activation, regulation or increasing gene expression (*i.e.*, increased protein levels of c-NOS). Of course, either or both of these mechanisms may be acting independently, consecutively, or simultaneously.

In one embodiment of the present invention there is provided a method for providing a sustained release administration of L-arginine or a biological equivalent of L-

arginine. The method allows a relatively constant release of arginine over a pre-determined amount of time. This is important due to what appears to be a supply-demand mismatch of L-arginine vis-à-vis NOS.

An alternative embodiment of the present invention provides a sustained release formulation comprised of L-arginine and an Hmg-CoA reductase inhibitor, preferably atorvastatin, pravastatin, or simvastatin, and more preferably pravastatin.

An alternative embodiment of the present invention provides a sustained release formulation comprised of L-arginine and an angiogenic growth factor. An alternative embodiment of the present invention provides a sustained release formulation comprised of L-arginine and DOX.

An alternative embodiment of the present invention provides a sustained release formulation comprised of an arginine based mixture, said arginine based mixture including a biological equivalent of arginine and an agent which enhances the bioavailability of nitric oxide. In a preferred embodiment of the present invention, the biological equivalent of arginine is L-arginine, the biological equivalent of arginine may be an arginase inhibitor, a nitrate, an angiogenic growth factor, DOX or an Hmg-CoA reductase inhibitor. The preferred Hmg-CoA reductase inhibitor is pravastatin.

Importantly, a slow release arginine formulation provides substantially constant release of L-arginine over a pre-determined period of time, thereby ameliorating the supply-demand mismatch involved with vasodilation or pathologies associated therewith.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1A is the top portion of a schematic representation of proposed L-arginine dependent and independent pathways;

Fig. 1B is the bottom portion flowing from Fig. 1A of a schematic representation of the proposed L-arginine dependent and independent pathways;

Fig. 2 is a bar graph illustrating the stimulation of NOS with pravastatin;

Fig. 3 is a graph illustrating the dissolution of 350 mg controlled release ethylcellulose core arginine tablets over time;

Fig. 4 is a graph illustrating the dissolution of 350 mg controlled release ethylcellulose core arginine tablets having a HPMC or Surelease® over time;

Fig. 5 is a graph illustrating the dissolution of 350 mg controlled release HPMC core arginine tablets over time;

Fig. 6 is a graph illustrating the dissolution of 350 mg controlled release HPMC core arginine tablets having a HPMC or Surelease® over time;

Fig. 7 is a graph illustrating the dissolution of 350 mg controlled release Kollidon® core arginine tablets over time

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The present provides the introduction of a therapeutic agent in a sustained or controlled release formulation which includes at least a NO precursor. More preferably the NO precursor is used in combination or in conjunction with an agent which enhances the conversion of the NO precursor to NO. Of particular interest as the NO precursor is L-arginine and its biological equivalents, especially L-arginine hydrochloride.

Depending on the intended use of the sustained release formulation, therapeutic agent(s) may be incorporated in a pill or tablet form or deposited in or coated on the body of a sustained release device (e.g. in a polymeric matrix). The sustained release formulation is preferably comprised of the NO precursor agent. The NO precursor agent in the sustained release formulation may be used with simultaneous or consecutive administration of other active agent (*e.g.*, a NOS agonist such as nitroglycerin or an Hmg-CoA reductase inhibitor such as pravastatin). By appropriate choice of the material for the sustained release formulation, a physiologically active amount of the NO precursor agent and/or therapeutic mixture may be

maintained for an extended period of time (e.g. one day and up to a week or more) depending on the form of administration and the acceptability of the this form. The amount of the NO precursor agent or therapeutic mixture has been and will be determined empirically in accordance with known techniques using animal and human models.

Fig. 1A and Fig. 1B illustrate a schematic representation of the proposed mechanism of action elicited by nitrovasodilators on both a generator cell and a target cell and their interrelationship. It appears that nitroglycerin or glycerol trinitrate's (GTN) mechanism of action is both L-arginine dependent and L-arginine independent and this implication has far reaching effects regarding the development and treatment of nitroglycerin tolerance and reducing clinical endpoints and mortality. Research into the area of NOS activation reveals a number of agonist of NOS some of which have been described in U.S. Pat. No. 5,543,430, U.S. Pat. No. 5,767,160, and U.S. Patent No. 5,968,983 all of which are hereby incorporated by reference in their entirety.

As shown in Figs. 1A and 1B the production of NO may result from a variety of sources and mechanisms which are discussed in detail in Ignarro, (Louis J. PhD., 1991, Pharmacology of Endothelium-Derived Nitric Oxide and Nitrovasodilators, The Western Journal of Medicine, pp.51-62.). Although this discussion focuses on smooth muscle and myocyte relaxation, cNOS, endothelial cells, and vascular smooth muscle cells, this illustration is not intended in any wayto imply any cellular relationship between the various sites of action, but rather meant to illustrate their proposed functional relationship. It is hypothesized herein and in related cases that the tolerance involves the L-arginine dependent pathway or endothelium dependent pathway shown in Figs. 1A and 1B. As seen in Fig. 1A, the generator cell is known to have several receptor mediated agonists such as Endothelium B receptor (ET_B); acetylcholine (Ach); substance P (SP), Histamine (H); arginine vasopressin (AVP); bradykinin (BK); Adenosine Triphosphate (ATP); Prostaglandin $F_{2\alpha}$ ($F_{2\alpha}$); Oxytocin, (OT); and the calcium ionophore (A23187) which stimulate the production of NOS.

Combining L-arginine or biologically equivalents thereto with an agent which enhances its conversion enhances the action of NO dependent response. For example, sustained administration (e.g., L-arginine four times daily) overcomes or ameliorates the resistance or

tolerance level normally seen when administering nitroglycerin alone. It is thought that sufficient L-arginine over a pre-determined time provides additioual substrate for the stimulated nitric oxide synthase which catalyzes the biotransformation of L-arginine into nitric oxide.

As shown in Fig. 1B, under conditions leading to tolerance the agonist effect of nitroglycerin on NOS induction leads to a depletion of L-arginine in the endothelial cell. By adding L-arginine when administering nitroglycerin or when tolerance is indicated it is believed that EDRF can be generated, and in the process a significant reduction in clinical and mortality endpoints can be obtained relative to using nitroglycerin alone or in combination with SNP or other donors of exogenous NO. Clinical data supports this proposition wherein treadmill time of individuals in nitate tolerance increased when they were given four times daily administratoin of L-arginine as compared to placebo.

In one embodiment of the invention, therapeutically effective amounts of L-arginine and inhibitors of Hmg-CoA reductase are mixed at a physiologically acceptable pH in a sustained release formulation and administered to a patient. Of course in the sustained release formulation the L-arginine may be formulated alone or in combination with the Hmg-CoA reductase inhibitor. If L-arginine is formulated alone in a sustained release formulation, the Hmg-CoA reductase inhibitor is administered in conjunction (e.g. consecutively, simultaneously, or within release period) of the sustained release L-arginine. A preferred Hmg-CoA reductase for this purpose is pravastatin. The fact that Hmg-CoA reductase may be agonist or stimulant of nitric oxide synthase has remarkable implications.

L-arginine may be used in conjunction with virtually any of the family of those substances known as Hmg-CoA reductase inhibitors. These are taught for example in U.S. Pat. Nos. 4,857,522, 5,190,970, and 5,461,039, all of which are hereby incorporated by reference for this teaching. Those particular Hmg-CoA reductase inhibitors most preferred for use in conjunction with the present formulation as selected from the group consisting of: atorvastatin, cerivastatin, simvastatin, lovastatin, pravastatin, compactin, fluvastatin, and dalvastatin. U.S. Patent No. 5,316,765 cites a number of these Hmg-CoA reductase inhibitors and is hereby incorporated by reference in its entirety. In particularly preferred embodiments of the present invention, the Hmg-CoA reductase inhibitor utilized is pravastatin, simvastatin, or atorvastatin.

In an even more particularly preferred embodiments, the administration of the present invention includes the Hmg-CoA reductase inhibitor pravastatin. Also within the scope of those Hmg-CoA reductase inhibitors of the present invention are included the bio-active metabolites of those Hmg-CoA reductase inhibitors described here, such as pravastatin sodium (the bio-active metabolite of mevastatin). Any one or several of the Hmg-CoA reductase inhibitor compounds may be mixed with L-arginine or substrate precursor to endogenous nitric oxide to provide a therapeutically effective mixture. This therapeutically effective mixture can then be incorporated into a sustained release formulation or other delivery device.

To demonstrate the levels of NO production, the direct effects of acteylcholine and pravastatin on NO production in bovine aortic endothelial cells (BAEC) was determined using a highly sensitive photometric assay for conversion of oxyhemoglobin to methemoglobin. NO oxidize; oxyhemoglobin (HbO_2) to methemoglobin (metHb) in the following reaction HbO_2 + NO - metHb + NO_3. The amount of NO produced by endothelial cells was quantified by measuring the change in absorbance as HbO_2 oxidizes to metHb. Oxyhemoglobin has a absorbance peak at 415 nm, while metHb has a 406 nm absorbance peak. By subtracting the absorbance of metHb from HbO_2, the concentration of NO can be assessed. The general method was patterned after that of *Feelisch et al.*, (Biochem. and Biophy. Res. Comm. 1991; 180, No I:286-293). Fig. 2 is a bar graph of the data generated which illustrates the effects of acetylcholine and pravastatin (10^{-6} and 10^{-5} M) administered for 3 min periods into the cell/bead perfusion system on NO production with: 1) 10^{-5} M L-arginine in control (basic) buffer, 2) 10^{-3} M of L-NAME in buffer, and 3) 10^{-3} M of L-arginine in buffer. Responses are transient elevations in NO production above basal levels. Data for responses in L-NAME and L-arginine augmented buffer are presented as percent of response in control buffer (100%); numbers in basic buffer bars indicate absolute production of NO in nmole *min. The remaining two bars denote differences between responses in L-NAME buffer vs both basic and L-arginine added buffers.

Many of the NOS agonists originally identified have also been implicated in angiogenesis. Substance P ("SP"), a secretory product, is identified herein as a cNOS agonist. Other secretory products (*e.g.*, those identified in "Macrophages and angiogenesis" by Sunderkotter et al. (J Leukoc Biol 1994 Mar; 55(3):410-22)) may also be expected to be agonists

of NOS. Bradykinin ("BK"), a NOS agonist, has also been implicated as a possible angiogenic factor. Angiogenic growth factors like those identified in Table I stimulate the growth of new blood vessels (*e.g.*, in vascular beds such as the coronary, peripheral, etc.) previously occluded with atherosclerotic obstructions. Angiogenic growth factors are proteins which were initially discovered as agents responsible for the growth of new blood vessels which maintain the growth and spread of cancerous tumors (neovascularization). Two of the angiogenic growth factors, vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF) result in the growth of significant new collateral blood vessels.

Like angiogenic agents Substance P and Bradykinin, VEGF and bFGF also appear to act as NOS agonists, specifically cNOS. It appears the resultant EDNO produced is in large part responsible for the new collateral vessel growth ("collateral") which in turn is responsible for the improvement in symptoms of ischemia seen in therapeutic angiogenesis. Furthermore, it has also been shown that the collateral responses to both VEGF and bFGF can be magnified significantly with L-arginine supplementation. Therefore, angiogenic growth factors, preferably VEGF and bFGF, appear to have dual applicability in the treatment of hypertension and cardiovascular diseases in that they both stimulate therapeutic angiogenesis and activity of Nitric Oxide Synthase. It also appears that the overall therapeutic angiogenic result with angiogenic growth factors is augmented to the extent they act as agonists of NOS. The fact that angiogenic growth factors are agonists or stimulators of nitric oxide synthase has important implications. Mixing angiogenic growth factors "in vitro" or "in vivo" with L-arginine may have an unforeseen beneficial effect that is associated with excess L-arginine providing additional substrate for NOS and the NOS being catalyzed to enzymatically increase the bio-transformation of L-arginine into nitric oxide (EDRF or EDNO) which would in turn amplify the overall therapeutic effect.

L-arginine may be used in conjunction with any of the family of those substances known as angiogenic growth factors. However, those particular angiogenic growth factors most preferred for use in conjunction with the present formulation are selected from the group consisting of VEGF and bFGF and even more preferably VEGF. Of course these agents may be over-expressed by administration of a particular agent in combination with a sustained release formulation of L-arginine. Although it is with particular reference to VEGF and bFGF it should

be noted that genetic over-expression of a NOS agonist or other bio-active agent as described herein is specifically acontemplated in combination with the controlled or sustained release of arginine. VEGF can be obtained from Genentech (South San Francisco, CA) and bFGF can be obtained from R&D Systems (Minneapolis, MN). The range of ratios of an angiogenic growth factor to L-arginine may be employed with virtually any of the angiogenic growth factors.

Compositions of the present invention may include agents such as a stabilizing compound, which may be administered in any sterile, bio-compatible pharmaceutical carrier, including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs or hormones. Pharmaceutically-acceptable carriers may also be comprised of excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA) hereby incorporated herein by reference in its entirety. The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc.

After the controlled release compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. Such labeling would include amount, frequency, and method of administration.

The exact dosage of the present invention will be determined by the practitioner, in light of factors related to the subject that requires treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy.

The theory and mechanism presented herein are provided solely to further elucidate the invention and in no way are meant to limit the scope of the claims. An alternative embodiment of present invention is based on a the fact that when cellular supply of L-arginine is

limited, NOS utilizes molecular oxygen as a lone substrate producing superoxide anion and other reactive free radicals which can lead to cardiovascular dysfunction and the pathogenesis of disease. Thus a sustained release formulation of arginine would appear to be very useful in ameliorating the conditions caused by depletion of L-arginine. The total intracellular concentration of L-arginine (0.1 - 1mM) in endothelial cells (EC) greatly exceeds the Km of eNOS for L-arginine. This suggests that eNOS is saturated with substrate and that levels of intracellular L-arginine are not limiting for NO production. However, other studies have shown that availability of L-arginine varies greatly within the EC due to intracellular compartmentalization and dequestration in addition to degradation by arginase or the presence of endogenous inhibitors of eNOS (i.e., asymmetrical dimethylarginine). Recently, it has also been shown that concurrent cellular L-arginine transport may be more important than intracellular L-arginine levels in providing L-arginine to NOS for NO production. Therefore, total intracellular concentration of L-arginine may not truly reflect the L-arginine available at the site of NOS action.

Supply of L-arginine may become limiting and reduce formation of NO in normal and pathological states. Treatment of guinea pigs with L-arginine has been shown to increase the duration of the vasodilatory response to acetylcholine under normal physiological conditions; prior stress with norepinephrine infusion accentuates this enhancement process. It has been demonstrated that acetylcholine and a Ca++ -ionophore which release NO can induce tolerance in isolated arterial rings. Tolerance was associated with depletion of L-arginine and was reversed with L-arginine repletion. L-arginine may also become limiting under pathologic conditions. Endothelial dysfunction in cardiomyopathic hamsters can be reversed by L-arginine. In addition, humans with acute hyperglycemia exhibit intense vasoconstriction and impaired endothelial function which can be completely reversed by intravenous infusions of low concentrations of LA. Other diseases in which pathology is attributed to a deficiency of L-arginine include hypertension, atherosclerosis, restenosis - post coronary angioplasty and reperfusion injury. Similarly, addition of L-arginine in these circumstances also ameliorates the deficit in endothelium-dependent relaxation.

Intracellular L-arginine is derived from several sources including the transport of L-arginine into cells, amount of intracellular L-citrulline recycled back to LA, rate of

degradation of L-arginine (arginase), incorporation of L-arginine into proteins (compartmentalization) and the amount of L-arginine utilized upon activation of intracellular NOS. Uptake of L-arginine into EC occurs through two carrier-mediated transporters and passive diffusion. The saturable carrier-mediated transporters include a sodium-dependent active transporter, system B + and a sodium-dependent transporter, system y+. The majority (80%) of L-arginine delivered into most cells is through the y^+ transporter. Regulation of L-arginine transport appears to involve cellular membrane potential.

When the balance of transporter regulatory factors is negative, L-arginine supply becomes limiting and subsequent production of $O_2^{\bullet-}$ may contribute to vascular and organ pathology. We compared the effects of NOS agonists and NO donors on L-arginine uptake by EC. Effects of NOS stimulation on superoxide anion production were also assessed in the presence and absence of L-arginine and the NOS antagonist, L-NAME.

It appears L-arginine levels are maintained primarily through the activity of the carrier-mediated Na^+-independent transporter, y^+, while the Na^+-dependent transporter, B^{o+}, and passive diffusion account for less than 15%. Concurrent transport of L-arginine to NOS may control NO production. However, L-arginine supply to NOS can be limiting due to compartmentalization within EC, arginase activity or utilization of L-arginine by NOS. We believe that NO and superoxide anion both appear to reduce the activity of the y^+ transporter and also reduce L-arginine available for NOS. Collectively, summation of supply verses demand or availability of L-arginine to NOS will determine whether NO or superoxide anion are formed.

Interestingly, data for the NO donor, SNAP, depicts initial stimulation of the y^+ transporter within 10 minutes followed by no change and then inhibition of cellular L-arginine uptake with more prolonged exposures to NO, a "cross-over" effect. An initial increase of cellular uptake of L-arginine is expected as NO is known to cause cellular hyperpolarization. However, longer exposures of 1 to 4 hours resulted in a marked reduction of L-arginine transport. These data were confirmed by using a different NO donor, DPTA, to stimulate prolonged exposure of cells to NO. DPTA releases NO slowly over time and, therefore, was used to repeat the longer durations of NO exposure.

It appears that concurrent L-arginine supply to NOS via system y^+, independent of overall intracellular L-arginine, is critical in establishing and maintaining vascular function. Factors including NOS agonists and NO itself appear to control y^+ activity and the summation of these factors is critical in determining NO and superoxide anion formation, both of which contribute to vascular dysfunction and disease.

The above-identified mechanism of action is provided to facilitate understanding of the present invention and is in no way meant to limit the scope of the present invention. The present invention is in no way limited in scope by the proposed mechanism of action.

Due to the apparent mismatch of available arginine a sustained release formulation of arginine (or a biological equivalent thereof) to be incorporated in a tablet, capsule, or other administration route would be advantageous. Arginine in a controlled release formulation in and of itself is an improvement over the state of the art in that it supplies a relatively constant amount of arginine and overcomes the large spiking present in instant release formulations. The supply-demand mismatch heightens the need for a slow or controlled L-arginine formulation.

The preferred embodiment of the present invention comprises extended-release tablets of an active ingredient which include a sustained release HPMC or ethylycellulose matrix. In a preferred embodiment of the present invention a combination comprising at least one active ingredient together with hydroxypropylmethylcellulose (HPMC) is mixed and is directly compressed to form tablets. Preferably, the composition is prepared by dry mixing the ingredients. Preferably, one of the active ingredients is arginine or a pharmacologically acceptable salt thereof, such as arginine hydrochloride or arginine sulfate, or a mixture thereof. More preferred as an active ingredient is L-arginine hydrochloride. Preferably about 15-50% of the active ingredient, based on the final weight of the tablets, is used; more preferably, about 20-50%; most preferably about 40-45%. In a preferred embodiment, the amount of active ingredient used is that which is sufficient to produce tablets, each comprising in the range of about 100mg to about 2g active ingredient, even more preferably about 100 mg to about 1g, even more preferably about 200 mg to about 500mg and most preferably about 350mg. In an alternate embodiment, the amount of active utilized is sufficient to produce tablets comprising about 750

mg of active ingredient each. A preferred HPMC is Methocel® K100M (produced by The Dow Chemical Co. of Midland, Mich.). Preferably about 20-40% HPMC is used, more preferably about 25-30% and most preferably about 28-29% HPMC.

Glidants, fillers, and other excipients that may be used in the preferred embodiments include those described, e.g., in Handbook of Pharmaceutical Excipients (J. C. Boylan et al., eds., 1986) and in H. A. Lieberman et al., Pharmaceutical Dosage Forms: Tablets (2d ed. 1990). Excipients generally may include: binders and adhesives; disintegrants, absorbents, and adsorbents; glidants and lubricants; fillers and diluents; and colorants, sweeteners, and flavoring agents. Preferred fillers include calcium salts and sugars, for example, calcium phosphates, calcium sulfates, mannitol, lactose, and mixtures thereof. More preferred fillers include dicalcium phosphate, tribasic calcium phosphate, directly compressible calcium sulfate, directly compressible mannitol, anhydrous lactose, flowable lactose (e.g., Fast Flo® lactose produced by Foremost Farms USA of Baraboo, Wis.), and mixtures thereof. Most preferred is dicalcium phosphate (Ca_2HPO). Preferably, about 20-40% by weight filler, based on the final weight of the tablets, is employed. However, where the filler consists of one or more sugars alone, preferably about 20-30% of filler is used.

Preferred glidants include colloidal silica and precipitated silica. A preferred colloidal silica is Cab-o-Sil® produced by the Cabot Corp. of Boston, Mass.; a preferred precipitated silica is Syloid® produced by W.R. Grace Co. of New York, N.Y. Preferably, about 0.2-2% by weight of glidant, based on the final weight of the tablets, is employed. Where colloidal silica alone is used, the tablets will preferably comprise about 0.2-0.8% by weight glidant, more preferably about 0.25-0.75%. Preferred lubricants include sodium lauryl sulfate, sodium stearyl fumarate, and metal stearates, alone or in combination with stearic acid. More preferred lubricants include magnesium stearate, zinc stearate, calcium stearate, and mixtures thereof, alone or in combination with stearic acid. Preferably about 0.2-2%, by final weight of the tablets, of lubricant is used, more preferably about 0.25-1.25%. For example, where magnesium stearate is the sole lubricant, the tablets preferably comprise about 0.3-0.5% lubricant; where a magnesium stearate-stearic acid mixture is used as the lubricant, about 0.25% magnesium stearate may be mixed with as much as about 1% stearic acid.

In the preferred embodiment mixing procedure, the active ingredient, e.g., arginine, sustained release polymer (e.g. HPMC, ethyl cellulose, Kollidon), and the filler, e.g., dicalcium phosphate dihydrate, are passed through a screen into a clean and dry blender, preferably in the order indicated. After mixing for 5 minutes, to the above mixture are added glidants, e.g. colloidal silicate, and this is then passed through a fine mesh screen and into a clean and dry blender. They are mixed for 5-20 minutes, following which a lubricant, e.g., magnesium stearate is screened into the blender and mixed in for an additional 5-15 minutes.

After the foregoing combination has been produced with thorough mixing, it is directly compressed to form tablets, i.e. any solid form, e.g., caplets. These are then coated with a pharmaceutically acceptable coating. Preferred coatings include cellulose ether-based coatings, such as HPMC-based coatings. A preferred coating is Opadry, produced by Colorcon, Inc. of West Point, Pa. Preferably about 0.54% by weight of coating is used (in terms of weight added to the uncoated tablet), more preferably about 1-2%. A wax, e.g., an edible wax such as carnauba wax may also be applied as a second coating thereover.

Numerous advantages result from the ability to use L-arginine in a sustained release dosage form. These include the use of smaller tablets which are more economical and are easy to administer. The cellulose ethers such as the hydroxypropylmethylcelluloses of the present invention are hydrophilic and tend to absorb moisture from the atmosphere. This is particularly important when the L-arginine form being used is moisture sensitive (or in the combination formulation when the agent or NOS agonist is moisture sensitive). When mixed with the active agent(s) (a biological equivalent of L-arginine alone or in combination with another agent), the mixture has excellent compressibility and the tablets prepared therefrom are hard and dense, have low friability and provide sustained release over an extended period.

The sustained release drug forms of the present invention are stable and the release rate does not change over an extended storage period. The therapeutic compositions of the present invention, in most cases, give a steady, reproducible release of the active medicament. The L-arginine compositions of the present invention can be formulated to act locally in the mouth or systemically. The L-arginine containing composition can be administered orally to transmit the active ingredients into the gastrointestinal tract and into the blood, fluids and tissues of the body without excessive peak concentrations occurring. Alternatively, the active ingredients can be formulated to act through the buccal tissues of the mouth to transmit the active ingredient directly into the blood stream thus avoiding first pass liver metabolism and by-passing the gastric and intestinal fluids which have an adverse inactivating or destructive action on many active ingredients unless they are especially protected against such fluids as by means of an enteric coating or the like. The active ingredient can also be of a type of medication which can be transmitted into the blood circulation through the rectal tissues. It is to be understood that the present invention is directed generally to an L-arginine (or biological equivalent) either alone or in combination in a sustained release formulation and thus is applicable to sublingual lozenges, suppositories and compressed tablets, the latter intended to be swallowed in unit dosage form and which upon ingestion according to a prescribed regimen give slow and regular release L-arginine.

In making up tablets containing an orally administrable systemically absorbable active component such as one of the heretofore mentioned, the oral carrier material is thoroughly intermixed with the L-arginine and other active ingredients which is also in powdered or granular form or in solution, and any other needed ingredients which are conventional in tablet making such as magnesium stearate, lactose, starch and, in general, binders, fillers, disintegrating agents and the like. The complete mixture, in an amount sufficient to make a uniform batch of tablets, e.g. 50,000, of which each contains an effective amount of active medicament, is then subjected to tableting in conventional tableting machines at compression pressures of 2000 to 16000 lbs/sq.in. and, because of the use of the specific carrier material of this invention in the production of the tablets, a product is obtained which has the desired hardness, low level of friability and a predetermined prolonged action and a regular delayed release pattern so that the

medicament is available over a period of 1 to 36 hours, depending on the precise tablet size, hardness and the particular carrier composition. In this way, it is possible to produce sustained or slow continuous release tablets in relatively simple and economical manner on a commercial scale as contrasted with the more elaborate and more complex materials and procedures heretofore employed or proposed.

The release pattern of active medicament from the carrier of the present invention can be controlled according to the particular medication and its intended therapeutic effect. For a sublingual lozenge or tablet, the release pattern may be varied from about 15 minutes to 4 hours. For orally administered tablets, the rate of release may be 2-4 hours, 4-8 hours, 8-10 hours, 10-12 hours, 12-15 hours, 15-18 hours, 20-24 hours, etc., as desired. For vaginal and rectal suppositories, the release pattern ranges from 2 to 36 hours, and can be less where indicated. Predetermined release patterns of unusually reliable and constant characteristics can be secured. This is often very important medically, especially when treating patients having coronary diseases, such as angina pectoris with nitroglycerin, or related problems of circulatory disorders or abnormal blood pressure

A number of controlled release prototypes were formulated to determine the most suitable for a controlled release arginine tablet or capsule. The excipient used to control the release of the active ingredient (e.g., L-arginine; its biological equivalent; or a combination of either or both of these with a NOS agonist) can be a variety of excipients commonly used in control release formulation. The two most common control release excipients are hydroxylproylmethylcellulose ("HPMC") and ethylcellulose . Preferably the tablets formed with these excipients are processed by direct compression, and even more preferably are coated with a control release film. The control release film slows the initial burst of active ingredient. The following illustrative examples are provided for a better understanding of the present invention and are non-limiting Variations will be obvious to those skilled in the art.

A typical formulation for the ethylcellulose base controlled release formulation is:

Ingredient	% by weight of Composition
L-Arginine	40-50% (e.g. 43.7%)
Ethylcellulose (e.g. Ethocel® 7 FP, Dow)	25-30%
DiCalcium Phosphate, Dihyrate	22-27%
Talc	1%
Magnesium Stearate	1%
Fumed Silica	1%

The ethylcellulose formulations demonstrate suitable, but less than ideal, flow and tablet weight variation. In an effort to ameliorate this glident levels and glident blending times were increased and ethylcellulose levels decreased. The dissolution data for Lots RB23 (30% ethylcellulose), RB24 (25% ethylcellulose) and RB25 (28% ethylcellulose) are shown in Figure 3. Arginine dissolution from these formulations is similar to the HPMC formulations.

Coating trials on the ethylcellulose tablets were also conducted. As discussed above, these coatings are designed to slow down arginine release from the tablets. As can be seen in Figure 4, HPMC and modified Surelease® tablet coating formulations were evaluated. The Surelease® coating had the desired effect and slowed arginine release of the 25% ET formulation (RB24) to a desirable profile similar to RB7. The HPMC coating levels tested, 4% and 6%, did little to slow down the initial arginine release. Higher HPMC coating levels therefore appear to be more suitable and a coating level of 10% HPMC would appear to be suitable.

A typical formulation for the Hydroxypropymethyl cellulose ("HPMC") based controlled release formulation is:

Ingredient	% by weight of Composition
L-Arginine	40-50% (e.g. 43.7%)
HPMC	28-30%
DiCalcium Phosphate	25-27%
Talc	1%
Magnesium Stearate	1%
Fumed Silica	.5%

The HPMC formulations have shown an extended arginine release profile. Figure 5 compares the reproducibility of the 30% HPMC (Lots RB1 & RB19) using the water insoluble dicalcium phosphate tablet binder. The two profiles are substantially the same. Lot RB20 shows the effect of changing to the water soluble tablet binder mannitol. This change dramatically speeds up Arginine dissolution from the tablet. Mannitol was selected, as it is a preferred diluent for a combination product (especially for the NOS agonist is IsoSorbide Mononitrate). The amount of mannitol used in Lot RB20 exceeds the amount contemplated for use in the combination product. Therefore, the release profile should not be as fast as shown in Figure 5.

Coating trials for the HPMC tablets were also conducted. As before, these coatings are designed to slow down arginine release from the tablets. As can be seen in Figure 6, HPMC and modified Surelease® tablet coating formulations were evaluated. The Surelease® coating slowed the initial arginine release. The 10% coating level delayed the onset of release while the 6% level significantly slowed the release in the first hour. Accordingly, it appears higher percentage HPMC levels would be more suitable.

Kollidon®, a relatively new controlled release excipient, was also tested. A 30% (RB21) and a 15% formulation (RB22b) were evaluated. Interestingly the 15% concentration had a slower dissolution profile than the 30%, see Figure 7. The 15% formula has a profile that

is similar to the uncoated 30% HPMC formulation. It would appear that coating samples of the 15% formulation with Surelease® at the 6-10% range would have a similar effect of slowing down arginine release as it does for the HPMC core.. It should be noted that the 30% formulation processed exceptionally well while for the 15% formulation it was difficult to obtain desirable tablet hardness. The tablet can be substantially reduced by using a sustained release formulation. This is due to the fact that L-arginine has a relatively fast half life in the bloodstream. Accordingly, a controlled release formulation of 350 mg may have the overall therapeutic impact of much larger doses (e.g. 1g). Accordingly a feasible tablet for ingestion can be manufactured. When one includes the agent which enhances the biotransformation of L-arginine (e.g. Imdar®) in a dose of 50 mg (assuming 80% active) with filler, and 350 mgs L-arginine the tablet can be formulated as an 400mg to about 1 gram size sustained release tablet.

The invention now being fully described in detail, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims. For example it may be beneficial to combine the HPMC with an alkali earth metal to slow the drug release from the tablet (e.g. sodium carbonate or any alkali metal salt of a carboxylic acid). Such variations are considered to be within the scope of the invention, which is intended to be limited only to the scope of the claims as interpreted according to the principles of patent law, including the doctrine of equivalents.

What is claimed is:

1. A method for producing extended-release tablets comprising the steps of:

mixing arginine with a sustained release matrix; and

compressing said mixture to form tablets.

2. The method of claim 1, wherein said L-arginine is selected from the group consisting of L-arginine hydrochlorie, pharmacologically acceptable arginine salts, and mixtures thereof.

3. The method of claim 1, wherein said arginine comprises about 15% to about 60% by weight of the tablet.

4. The method of claim 1, wherein said arginine is present in an amount sufficient to produce tablets in a range from about 150 mg to about 2000 mg of said L-arginine.

5. The method of claim 1, wherein said active ingredient is present in an amount sufficient to produce tablets with about 750 mg of L-arginine.

6. The method of claim 1, wherein said arginine is present in an amount sufficient to produce tablets with about 350 mg L-arginine.

7. The method of claim 1, wherein said L-arginine and said sustained release matrix are dry mixed with a glidant and a filler.

8. The method of claim 7, wherein said glidant is selected from the group consisting of colloidal silica, precipitated silica, and mixtures thereof.

9. The method of claim 1, wherein said sustained release matrix is hydroxypropylmethylcellulose (HPMC).

10. The method of claim 1, wherein said tablet is coated with a coating, said coating being a cellulose ether-based coating alone or in combination with ethyl celhilose.

11. The method of claim 1, further including the step of mixing in an agent which enhances the bio-transformation of L-arginine into Nitric Oxide.

12. The method of claim 11, wherein said agent is selected from the group consisting of a NOS agonist, an HMG-CoA reductase inhibitor, and an ACE inhibitor.

13. A composition comprised of:
arginine; and
a sustained release polymeric matrix.

14. The composition of claim 13, further including a nitrate,

15. The composition of claim 13, further including an Hmg-CoA reductase inhibitor.

16. An extended-release pharmaceutical tablet comprised of a sustained release matrix and arginine.

17. The tablet of claim 16, further including an agent which enhances the bio-transformation of arginine into Nitric Oxide.

18. The tablet of claim 17, wherein said agent is selected from the group consisting of a NOS agonist, a nitrate, an HMG-CoA reductase inhibitor, an ACE inhibitor, a nutraceutical.

19. The tablet of claim 18, wherein said arginine is about 20% to about 60% by weight of said tablet.

20. The tablet of claim 16, wherein said arginine is selected from the group consisting of L-arginine, L-arginine hydrochloride, pharmacologically acceptable arginine salts, and mixtures thereof.

ABSTRACT

A sustained release formulation of L-arginine alone or in combination with an agent which enhances the biotransformation of L-arginine into NO is described herein.

FIGURE 1A

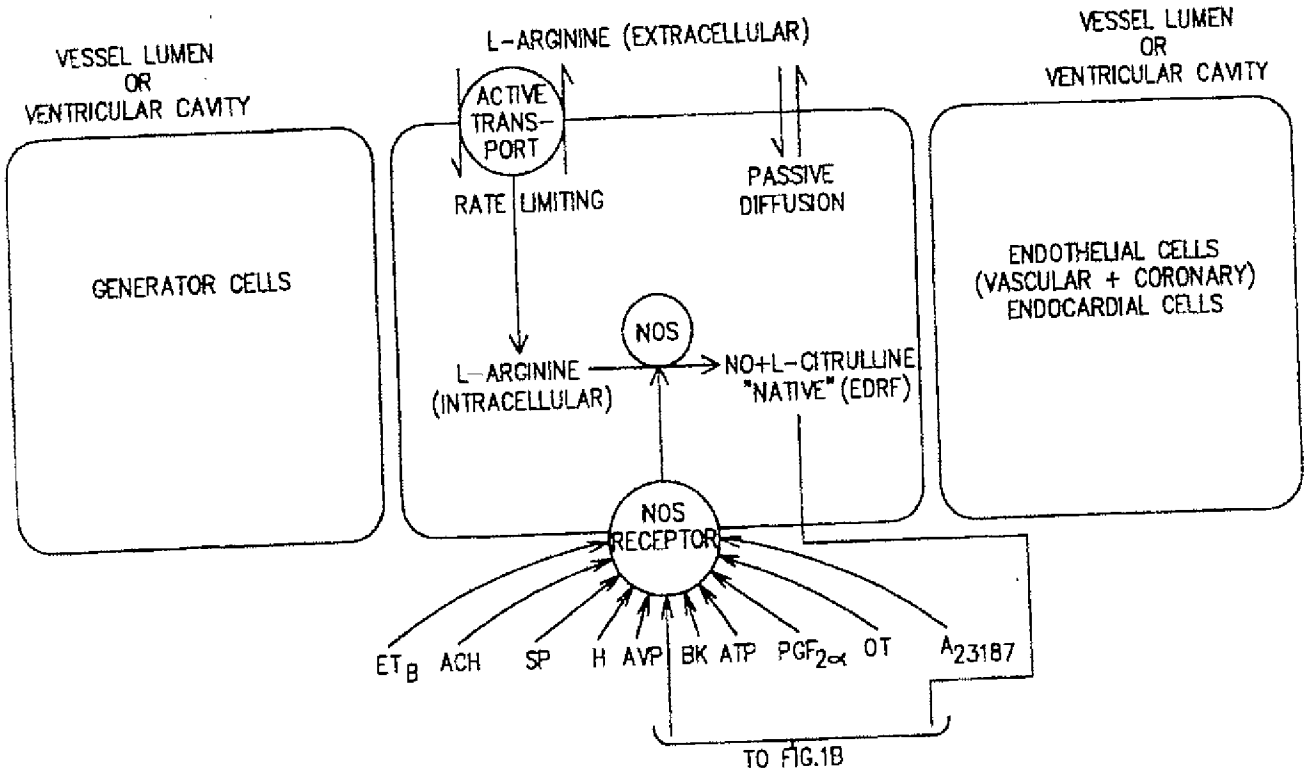


FIGURE 1B

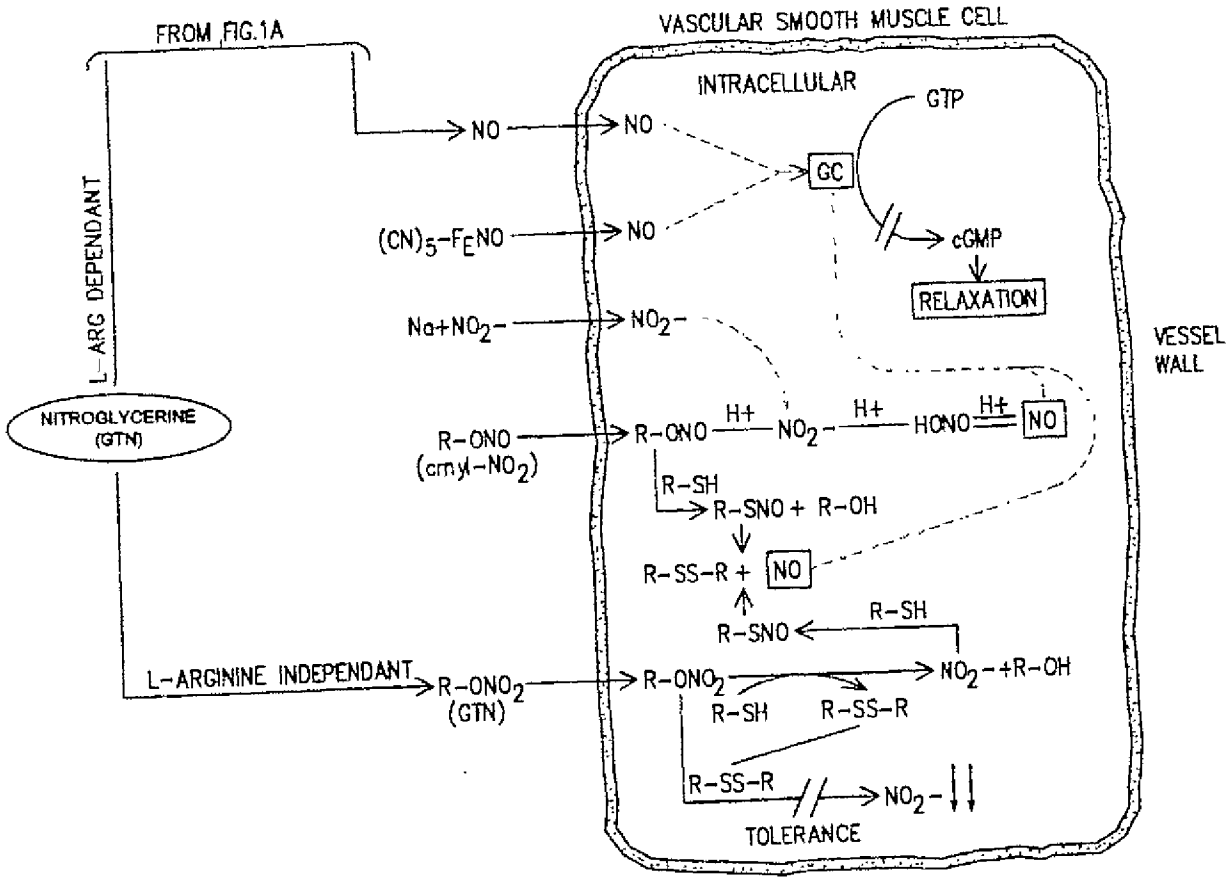
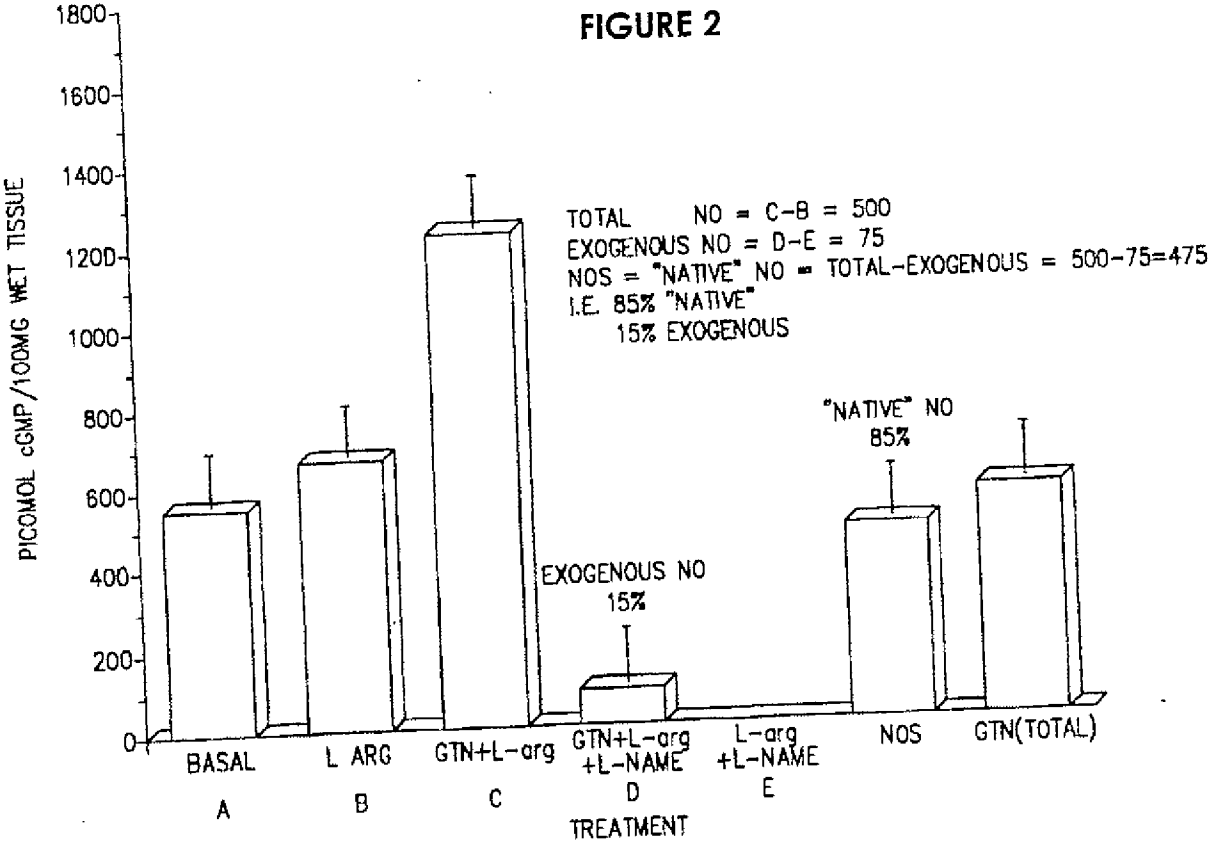


FIGURE 2



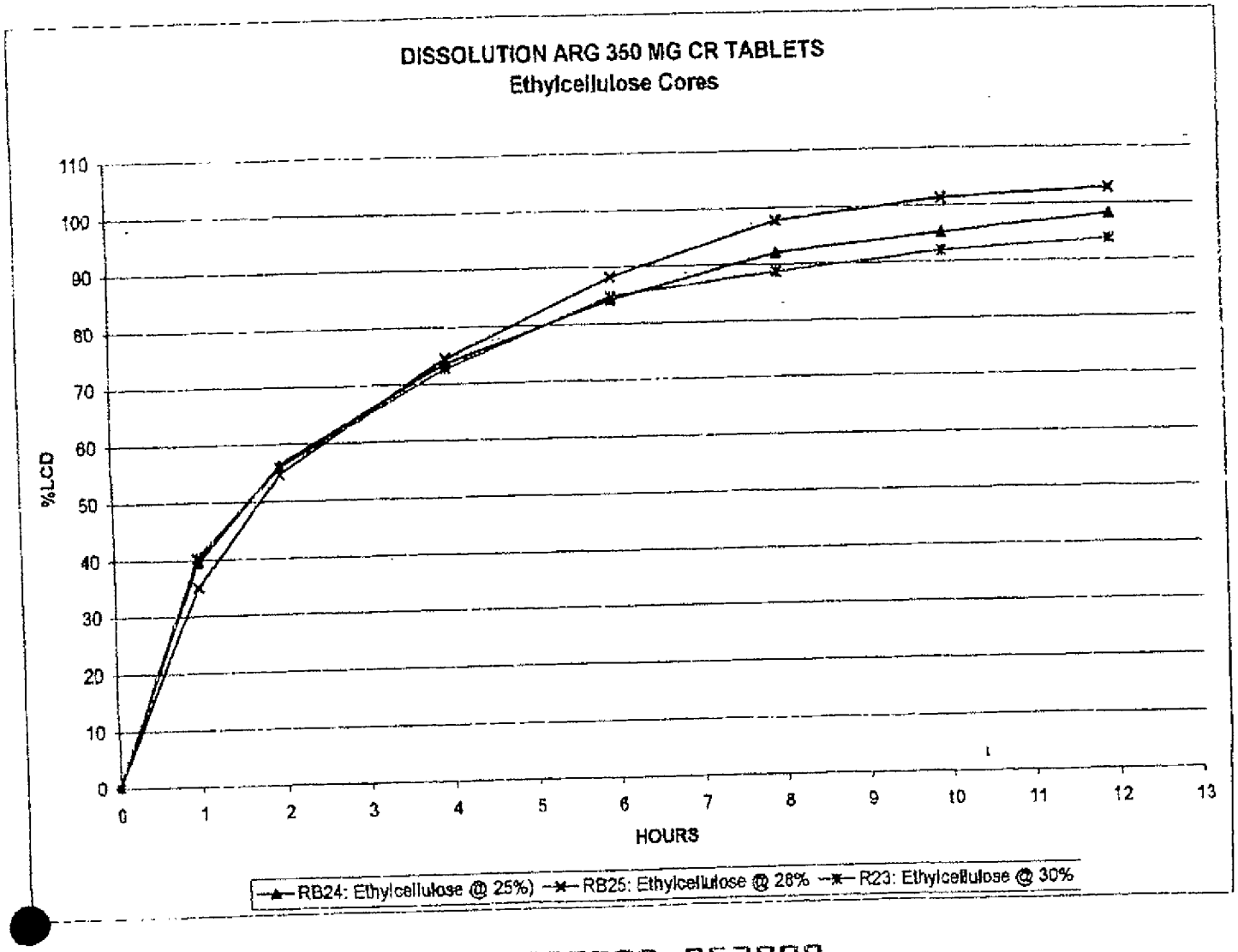


Figure 3

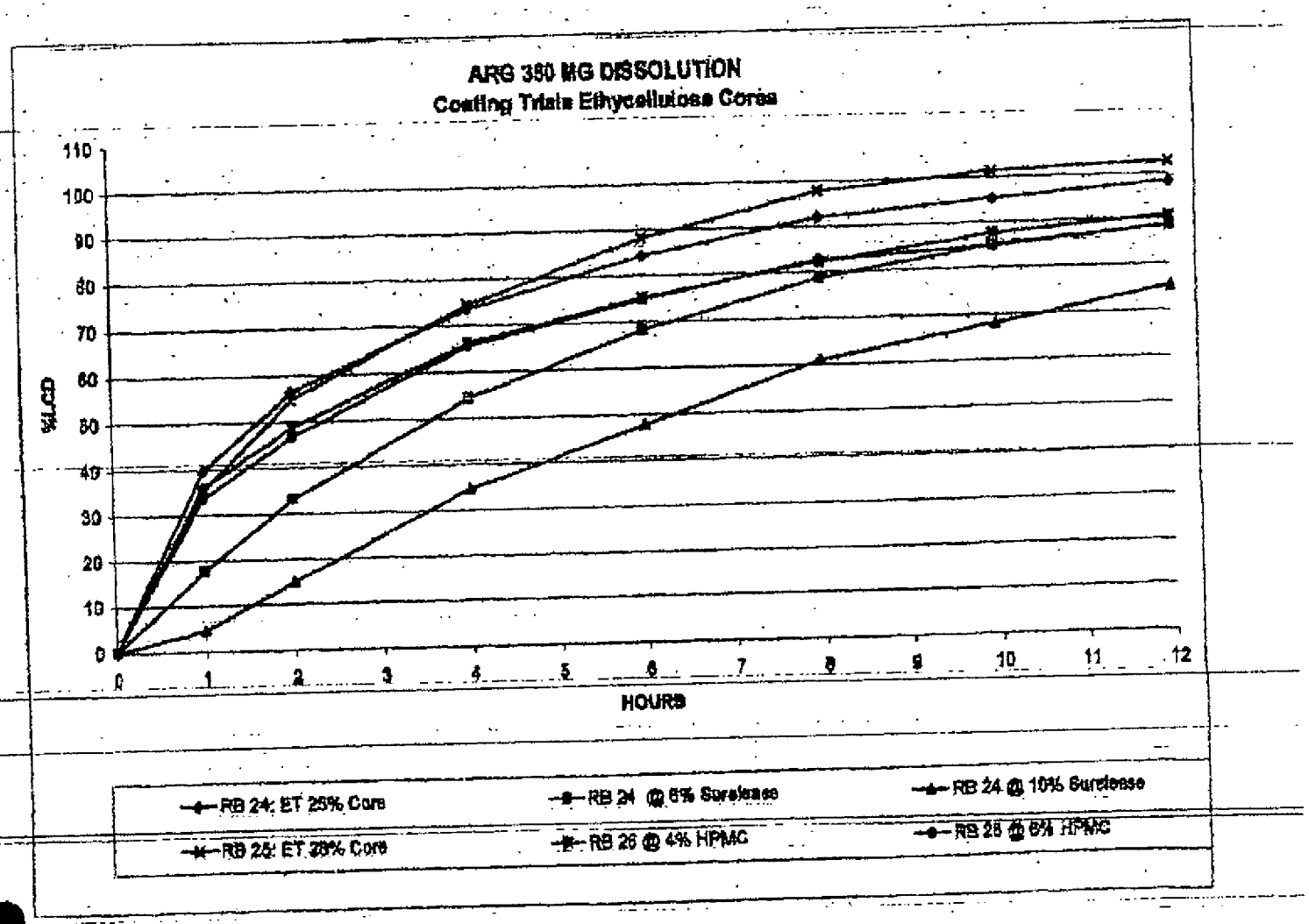


Figure 4

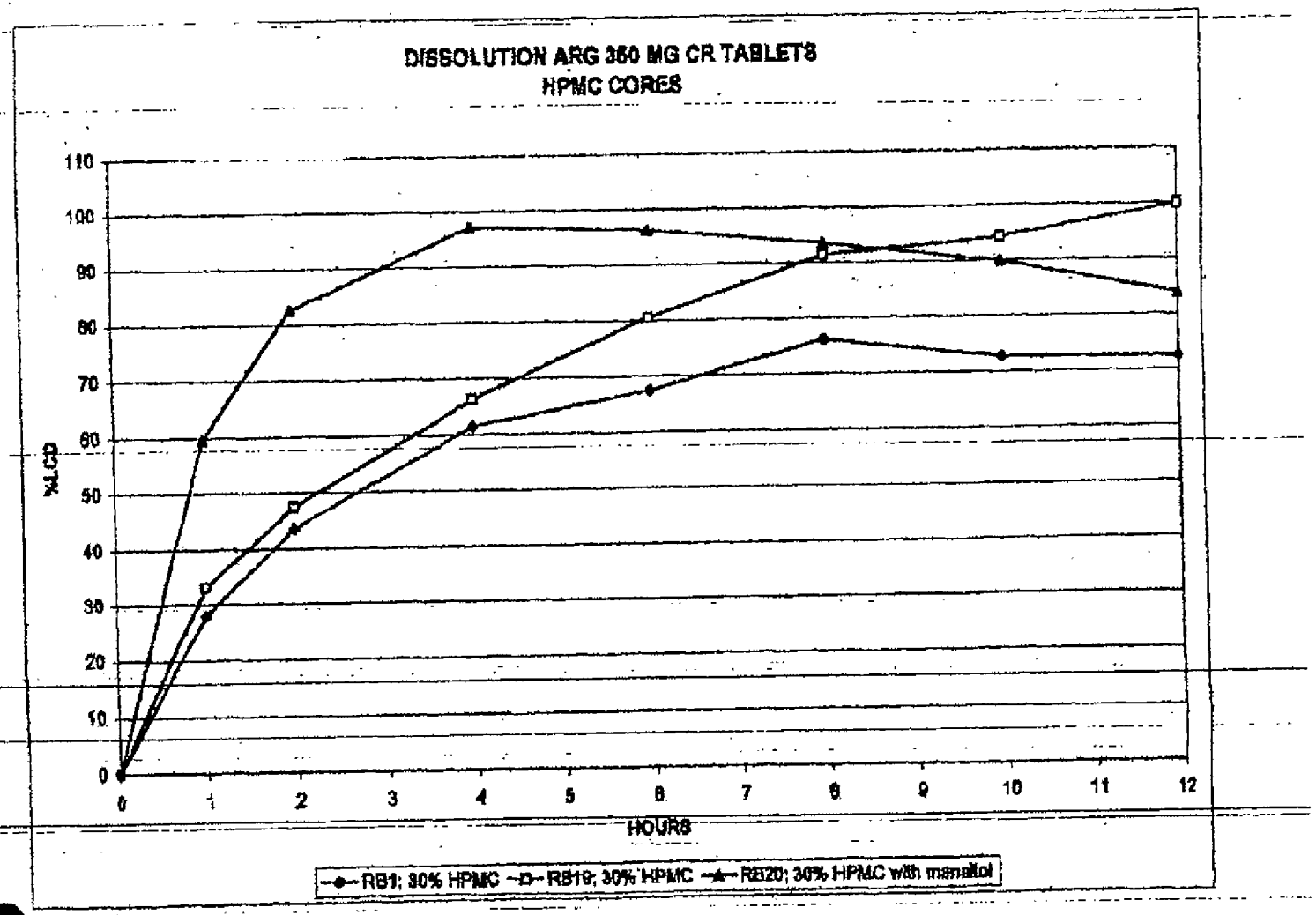


Figure 5

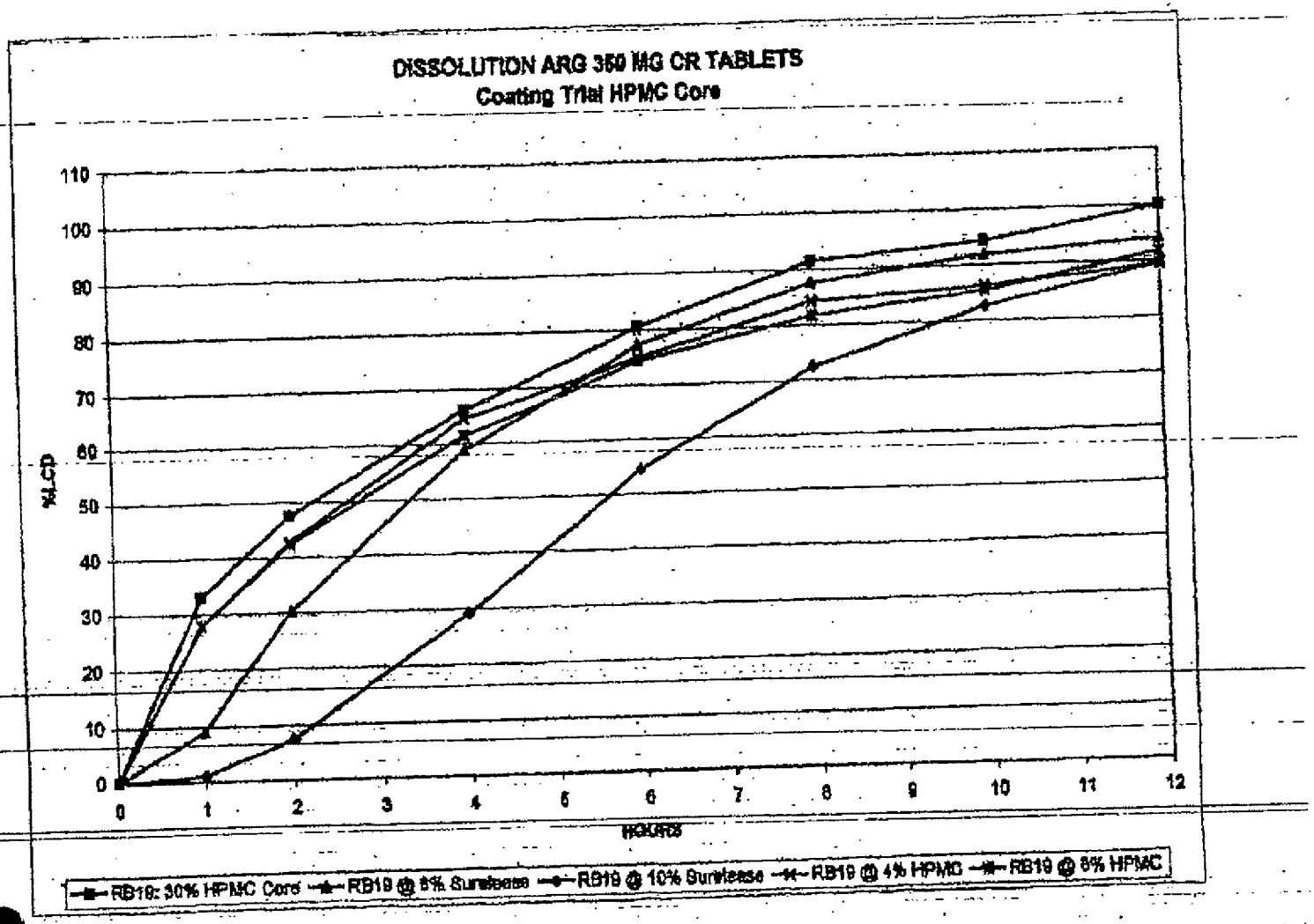


Figure 6

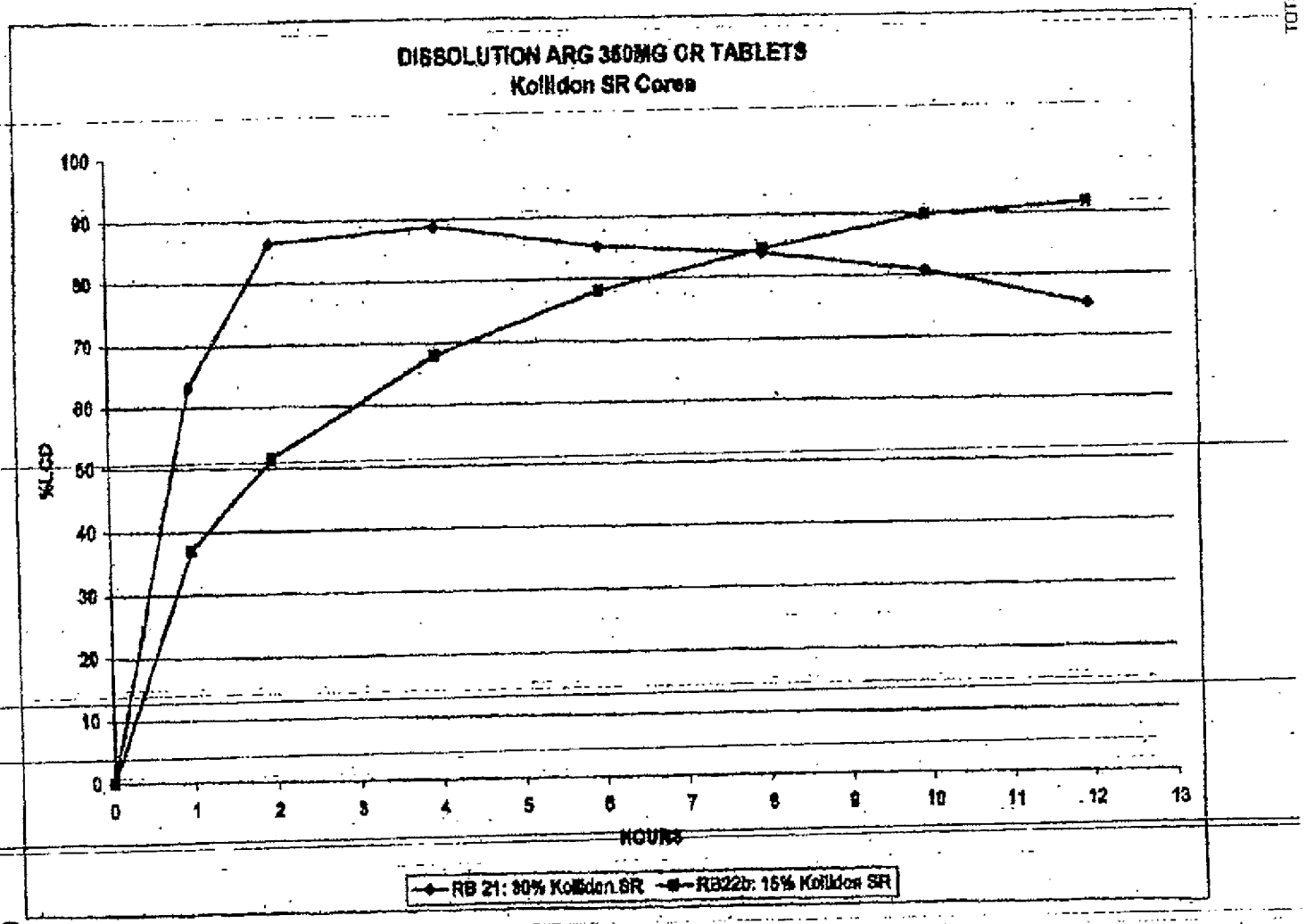


Figure 7

EXHIBIT Q
FOLLOWS

UNITED STATES PATENT AND TRADEMARK OFFICE

25 AUG 2009

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United States Patent and Trademark Office
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Alexandria, VA 22313-1450
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AUG 27 2009

PEPPER HAMILTON LLP
ONE MELLON CENTER, 50TH FLOOR
500 GRANT STREET
PITTSBURGH PA 15219

In re Application of KAESEMEYER
Application No.: 10/258,633
Filing Date: 24 October 2002
Attorney Docket No.: 126625.00710
For: CONTROLLED RELEASE ARGININE FORMULATIONS

: DECISION ON PETITION
: UNDER 37 CFR 1.78(a)(3)

This is a decision on the petition under 37 CFR 1.78(a)(3), filed 06 May 2009 to accept an unintentionally delayed claim under 35 U.S.C. §120 for the benefit of priority to the nonprovisional application identified in the concurrently filed amendment to the specification. The petition is **DISMISSED**.

A petition for acceptance of a claim for late priority under 37 CFR 1.78(a)(3) is only applicable to those applications filed on or after November 29, 2000. Further, the petition is appropriate only after the expiration of the period specified in 37 CFR 1.78(a)(2)(ii). In addition, the petition under 37 CFR 1.78(a)(3) must be accompanied by:

(1) the reference required by 35 U.S.C. § 120 and 37 CFR 1.78(a)(2)(i) of the prior-filed application, unless previously submitted;
(2) the surcharge set forth in § 1.17(t); and
(3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2)(ii) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional.

The instant petition does not comply with item (1).

37 CFR 1.78(a)(2)(i) requires that any nonprovisional application claiming the benefit of one or more prior-filed copending nonprovisional applications must contain or be amended to contain a reference to each such prior-filed application, identifying it by application number (consisting of the series code and serial number) and indicating the relationship of the applications. The relationship between the applications is whether the subject application is a continuation, divisional, or continuation-in-part of a prior-filed nonprovisional application. An example of a proper benefit claim is: "This application is a U.S. national stage of international application PCT/US2001/20887 (WO 02/00212) filed June 28, 2001, which is a continuation in part of U.S. Application number 09/605,599, filed June 28, 2000." The reference added to the specification does not comply with 37 CFR 1.78(a)(2)(i) since the proper relationship, which includes the type of continuing application, is not stated. See Manual of Patent Examining Procedure, (8th ed., Revision 7 (July 2008)), Section 201.11, Reference to Prior Application(s). The amendment filed 06 May 2009 is improper because there is no specific reference indicating the relationship of

international application PCT/US 2007/20887 to application 09/605,599. Even though the application data sheet filed with the petition states a proper relationship, the petition cannot be granted due to the improper amendment to the specification.

The reference to add the prior-filed applications on page one following the first sentence of the specification is not acceptable as drafted since it improperly incorporates by reference the prior-filed applications. An incorporation by reference statement added after an application's filing date is not effective because no new matter can be added to an application after its filing date (*see* 35 U.S.C. § 132(a)). If an incorporation by reference statement is included in an amendment to the specification to add a benefit claim under 35 U.S.C. § 120 after the filing date of the application, the amendment would not be proper. When a benefit claim under 35 U.S.C. § 120 is submitted after the filing of an application, the reference to the prior application cannot include an incorporation by reference statement of the prior application. *See* Dart Industries v. Banner, 636 F.2d 684, 207 USPQ 273 (C.A.D.C. 1980). *Note* MPEP §§ 201.06(c) and 608.04(b).

Accordingly, before the petition under 37 CFR § 1.78(a)(3) can be granted, a renewed petition under 37 CFR § 1.78(a)(3) and a substitute amendment[1] or supplemental application data sheet (37 CFR 1.76) stating the relationship of the prior-filed application to PCT/US2001/020887 is required.

Further correspondence with respect to this matter should be addressed as follows:

By mail: Mail Stop PCT LEGAL ADMINISTRATION
Commissioner for Patents
Post Office Box 1450
Alexandria, VA 22313-1450

By hand: Customer Window located at:
Mail Stop PCT
Randolph Building
401 Dulany Street
Alexandria, VA 22314

By fax: 571-273-0459
ATTN: Office of PCT Legal Administration

Any questions concerning this matter may be directed to Cynthia Kratz at (571) 272-3286.

Byran Lin
PCT Legal Examiner
Office of PCT Legal Administration

[1] *Note* 37 CFR 1.121

EXHIBIT R
FOLLOWS

PATENT APPLICATION
Application No. 10/258,633
Attorney Docket No. 126625.00710

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/258,633
Applicant	:	Wayne H. Kaesemeyer
Filed	:	May 6, 2003
Group Art Unit	:	1618
Examiner	:	James William Rogers
Docket No.	:	126625.00710
Confirmation No.	:	3645

Title: CONTROLLED RELEASE ARGININE FORMULATIONS

REQUEST FOR RECONSIDERATION OF PETITION TO ACCEPT AN UNINTENTIONALLY DELAYED CLAIM OF PRIORITY UNDER 37 C.F.R. §1.78(a)(3)

Mail Stop PCT LEGAL ADMINSTRATION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA. 22313-1450

Examiner:

Applicant respectfully requests that the claim of priority recited in the first paragraph of the specification of the above-referenced application be amended pursuant to 37 C.F.R. §1.78(a)(2)(i) and (ii) to include the claim of priority to U.S. Non-Provisional Application No. 09/605,599 (hereinafter the "'599 Application"), filed June 28, 2000. Applicant previously submitted the priority document for the '599 Application with the Petition filed May 6, 2009. The amended claim of priority stating the relationship of the '599 Application as a continuation of PCT/US2001/20887 is presented on page 3 of this Petition. A Supplemental Application Data Sheet (hereinafter "ADS") stating the relationship of the prior-filed applications to the instant application in compliance with 37 C.F.R. §1.78(a)(2)(i) is submitted herewith.

Pursuant to 37 C.F.R. §1.78(a)(2)(i) and (ii), a reference to be included in the specification claiming benefit of prior applications must be submitted during the pendency of the application, which requirement is met in the present circumstances. However, the present benefit

claim is being presented after the time period provided by 37 C.F.R. §1.78(a)(2)(ii). Accordingly, Applicant hereby petitions the Commissioner under 37 C.F.R. §1.78(a)(3) to accept the present unintentionally delayed benefit claim.

Upon grant of this Petition, Applicant hereby requests an updated filing receipt identifying the proper priority claim of the instant application.

No fee is believed to be due for this submission. However, the Commissioner is hereby authorized to charge any additional payment of fee or credit any overpayment or refund to Deposit Account No. 50-0436.

Respectfully Submitted,

By: N. Nicole Endejann
Reg. No. 50,229

Pepper Hamilton LLP
One Mellon Center, 50th Floor
500 Grant Street
Pittsburgh, PA 15219
Telephone No.: (412) 454-5869
Facsimile No.: (412) 281-0717
Date: September 18, 2009

AMENDMENT TO SPECIFICATION - PRIORITY CLAIM

Please amend the first paragraph after the title "RELATED APPLICATION DATA" on page 1 of the specification as follows:

This application is a U.S. national stage of international application PCT/US2001/20887 (WO 02/00212) filed June 28, 2001, which is a continuation of U.S. Application No. 09/605,599 filed June 28, 2000, now abandoned, ~~This application~~ which is a continuation-in-part application of U.S. Serial No. ~~09/239,392~~ 09/293,392 filed April 16, 1999, now U.S. Patent No. 6,425,881 dated July 30, 2002, which is a continuation-in-part application of U.S. Serial No. 09/226,580 filed January 7,1999, now U.S. Patent No. 6,239,172 dated May 29, 2001, which is a continuation-in-part application of U.S. Serial No. ~~09/833,842~~ 08/833,842 filed April 10, 1997, now U.S. Patent No. 5,968,983 dated October 19, 1999, which is a continuation-in-part application of U.S. Serial No. 08/693,882 filed August 5, 1996, now U.S. Patent No. 5,767,160 dated ~~August 6, 1996~~ June 16, 1998, which is a continuation-in-part application of U.S. Serial No. 08/321,051 filed October 5,1994, now U.S. Patent No. 5,543,430 dated ~~June 16,1998~~ August 6, 1996.

SUPPLEMENTAL

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	126625.00710
	Application Number	10/258,663
Title of Invention	CONTROLLED RELEASE ARGININE FORMULATIONS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Wayne	H.	Kaesemeyer	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Augusta	State/Province	GA	Country of Residence	US

Citizenship under 37 CFR 1.41(b): US

Mailing Address of Applicant:

Address 1	1021 15th Street		
Address 2			
City	Augusta	State/Province	GA
Postal Code	30901	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ An Address is being provided for the correspondence Information of this application.

Customer Number	21269		
Email Address	docketingpgh@pepperlaw.com	Add Email	Remove Email

Application Information:

Title of the Invention	CONTROLLED RELEASE ARGININE FORMULATIONS		
Attorney Docket Number	126625.00710	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	8	Suggested Figure for Publication (if any)	

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	126625.00710
	Application Number	
Title of Invention	CONTROLLED RELEASE ARGININE FORMULATIONS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Wayne	H.	Kaesemeyer	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Augusta	State/Province	GA	Country of Residence	US

Citizenship under 37 CFR 1.41(b) US

Mailing Address of Applicant:

Address 1	1021 15th Street		
Address 2			
City	Augusta	State/Province	GA
Postal Code	30901	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ An Address is being provided for the correspondence Information of this application.

Customer Number	21269		
Email Address	docketingpgh@pepperlaw.com	Add Email	Remove Email

Application Information:

Title of the Invention	CONTROLLED RELEASE ARGININE FORMULATIONS		
Attorney Docket Number	126625.00710	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	8	Suggested Figure for Publication (if any)	

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	126625.00710
	Application Number	
Title of Invention	CONTROLLED RELEASE ARGININE FORMULATIONS	

Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	**Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application has not and wttt not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	21269		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	a 371 of international	PCT/US2001/20887	2001-06-28
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US2001/20887	Continuation of ~~CIP of~~	09605599	2000-06-28
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
09605599	Continuation in part of	09293392	1999-04-16	6425881	2002-07-30
Prior Application Status	Patented			Remove	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
09293392	Continuation in part of	09226580	1999-01-07	6239172	2001-05-29
Prior Application Status	Patented			Remove	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
09226580	Continuation in part of	08833842	1997-04-10	5968983	1999-10-19
Prior Application Status	Patented			Remove	

PTO/SB/14 (07-07)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	126625.00710
	Application Number	
Title of Invention	CONTROLLED RELEASE ARGININE FORMULATIONS	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
08833842	Continuation in part of	08693882	1996-08-05	5767160	1998-06-16

Prior Application Status: Patented — Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
08693882	Continuation in part of	08321051	1994-10-05	5543430	1996-08-06

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			○ Yes ○ No

Additional Foreign Priority Data may be generated within this form by selecting the Add button.

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1

If the Assignee is an Organization check here. ☒

Organization Name	PALMETTO PHARMACEUTICALS, LLC		
Mailing Address Information:			
Address 1	217 MEDINAH		
Address 2			
City	SAINT SIMONS ISLAND	**State/Province**	GA
Country	US	Postal Code	31522
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the Add button.

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/N. Nicole Endejann/			Date (YYYY-MM-DD)	2009-05-06
First Name	N. Nicole	Last Name	Endejann	Registration Number	50229

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	126625.00710
	Application Number	
Title of Invention	CONTROLLED RELEASE ARGININE FORMULATIONS	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissionar for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

EXHIBIT S
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UNITED STATES PATENT AND TRADEMARK OFFICE

08 DEC 2009

Commissioner for Patents
United States Patent and Trademark Office
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Alexandria, VA 22313-1450
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PEPPER HAMILTON LLP
ONE MELLON CENTER, 50TH FLOOR
500 GRANT STREET
PITTSBURGH PA 15219

In re Application of KAESEMEYER
Application No.: 10/258,633
Filing Date: 24 October 2002
Attorney Docket No.: 126625.00710
For: CONTROLLED RELEASE ARGININE FORMULATIONS

: DECISION ON PETITION
: UNDER 37 CFR 1.78(a)(3)

This is a decision on the petition under 37 CFR 1.78(a)(3), filed 18 September 2009 to accept an unintentionally delayed claim under 35 U.S.C. §120 for the benefit of priority to the nonprovisional application identified in the concurrently filed amendment to the specification. The petition is **DISMISSED**.

A petition for acceptance of a claim for late priority under 37 CFR 1.78(a)(3) is only applicable to those applications filed on or after November 29, 2000. Further, the petition is appropriate only after the expiration of the period specified in 37 CFR 1.78(a)(2)(ii). In addition, the petition under 37 CFR 1.78(a)(3) must be accompanied by:

(1) the reference required by 35 U.S.C. § 120 and 37 CFR 1.78(a)(2)(i) of the prior-filed application, unless previously submitted;
(2) the surcharge set forth in § 1.17(t); and
(3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2)(ii) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional.

The instant petition does not comply with item (1).

MPEP 201.11, Section III. C., states in relevant part,

Sometimes a pending application is one of a series of applications wherein the pending application is not copending with the first filed application but is copending with an intermediate application entitled to the benefit of the filing date of the first application...Appropriate references must be made in each intermediate application in the chain of prior applications. If an applicant desires, for example, the following benefit claim: "this application is a continuation of Application No. C, file —, which is a continuation of Application No. B, filed —, which claims the benefit of provisional Application A, filed —," then Application No. C must have a reference to Application No. B and provisional application No. A, and Application No. B must have a reference to provisional Application No. A (Emphasis added.)

In the present case, the first paragraph of the specification has been amended to state that U.S. Application Number 09/605,599 is a continuation in part of U.S. Application Number

09/293,392. However, a review of Office records indicates that U.S. Application Number 09/605,599 does not contain an appropriate reference to U.S. Application Number 09/293,392. Accordingly, the amendment to the specification is not acceptable at the present time. The application data sheet filed with the renewed petition is defective for the same reason. Applicant is further advised that any supplemental application data sheet must be titled as such. See 37 CFR 1.76(c)(2).

Accordingly, before the petition under 37 CFR § 1.78(a)(3) can be granted, U.S. application 09/605,599 must be amended to include the necessary reference as discussed above.

Further correspondence with respect to this matter should be addressed as follows:

By mail: Mail Stop PCT LEGAL ADMINISTRATION
Commissioner for Patents
Post Office Box 1450
Alexandria, VA 22313-1450

By hand: Customer Window located at:
Mail Stop PCT
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By fax: 571-273-0459
ATTN: Office of PCT Legal Administration

Any questions concerning this matter may be directed to Cynthia Kratz at (571) 272-3286.

Byran Lin
PCT Legal Examiner
Office of PCT Legal Administration

EXHIBIT T
FOLLOWS

RELATED APPLICATION FAMILY DIAGRAM